

Single Technology Appraisal

Upadacitinib for treating giant cell arteritis [ID6299]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Upadacitinib for treating giant cell arteritis [ID6299]

Contents:

The following documents are made available to stakeholders:

Access the [final scope](#) and [final stakeholder list](#) on the NICE website.

1. **Company submission** from AbbVie
 - a. Company submission
 - b. Submission addendum
 - c. Submission addendum cover letter
2. **Company summary of information for patients (SIP)** from AbbVie
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
 - a. PMRGCA UK (Polymyalgia, Rheumatica & Giant Cell Arteritis UK)
 - b. Vasculitis UK
 - c. British Society for Rheumatology – *written by clinical expert Dr Fiona Coath*
5. **Expert personal perspectives** from:
 - a. Dr Sarah Mackie – clinical expert, nominated by PMRGCA UK
 - b. Dr Fiona Coath – clinical expert, nominated by the British Society for Rheumatology
 - c. Fiona Johnson – patient expert, nominated by PMRGCA UK
 - d. Maxine Wright – patient expert, nominated by Vasculitis UK
6. **External Assessment Report** prepared by Birmingham Centre for Evidence and Implementation Science
7. **External Assessment Report – factual accuracy check**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Upadacitinib for giant cell arteritis [ID6299]

Company evidence submission

May 2025

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Contents

Contents	2
Tables and figures	5
Executive summary	8
1 Decision problem, description of the technology and clinical care pathway	10
1.1 Decision problem	10
1.2 Description of the technology being evaluated	16
1.3 Health condition and position of the technology in the treatment pathway ..	18
1.3.1 Disease overview	20
1.3.2 Clinical pathway	32
1.3.3 Unmet need	37
1.3.4 Upadacitinib treatment for giant cell arteritis	38
1.4 Equality considerations	40
2 Clinical effectiveness	42
2.1 Identification and selection of relevant studies	44
2.2 List of relevant clinical effectiveness evidence	44
2.3 Summary of methodology of the relevant clinical effectiveness evidence ..	46
2.3.1 SELECT-GCA methodology	46
2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence	60
2.5 Critical appraisal of the relevant clinical effectiveness evidence	60
2.6 Clinical effectiveness results of the relevant studies	61
2.6.1 SELECT-GCA efficacy	61
2.7 Subsequent treatments used in the relevant studies	71
2.8 Subgroup analysis	71
2.9 Meta-analysis	74
2.10 Indirect and mixed treatment comparisons	74
2.11 Adverse reactions	74
2.11.1 Safety analysis set in period 1 (SS1)	74
2.11.2 Long-term safety analysis set (SS_LT)	87
2.12 Ongoing studies	99
2.13 Interpretation of clinical effectiveness and safety evidence	99
2.13.1 Principal findings from the clinical evidence	99
2.13.2 Strengths and limitation of the clinical evidence base	101
3 Cost effectiveness	104
3.1 Published cost-effectiveness studies	106
3.2 Economic analysis	110
3.2.1 Patient population	110
3.2.2 Model structure	111
3.2.3 Intervention technology and comparators	117

3.3	Clinical parameters and variables	118
3.3.1	Transition probabilities.....	118
3.3.2	Corticosteroid dose.....	127
3.3.3	Treatment duration	135
3.3.4	Efficacy waning post treatment discontinuation.....	136
3.3.5	Adherence.....	136
3.4	Measurement and valuation of health effects	137
3.4.1	Health-related quality-of-life studies.....	137
3.4.2	Health-related quality-of-life data from clinical trials.....	141
3.4.3	Mapping	143
3.4.4	Health-related quality-of-life data used in the cost-effectiveness analysis	143
3.5	Cost and healthcare resource use identification, measurement and valuation	147
3.5.1	Intervention and comparators' costs and resource use.....	148
3.5.2	Health-state unit costs and resource use	150
3.5.3	Adverse reaction unit costs and resource use.....	154
3.5.4	Miscellaneous unit costs and resource use	156
3.6	Severity.....	157
3.7	Uncertainty	157
3.8	Managed access proposal.....	158
3.9	Summary of base-case analysis inputs and assumptions.....	158
3.9.1	Summary of base-case analysis inputs	158
3.9.2	Assumptions	161
3.10	Base-case results.....	163
3.10.1	Base-case incremental cost-effectiveness analysis results	163
3.11	Exploring uncertainty	165
3.11.1	Probabilistic sensitivity analysis	165
3.11.2	Probabilistic sensitivity analysis results	168
3.11.3	Deterministic sensitivity analysis.....	170
3.11.4	Scenario analysis.....	172
3.12	Benefits not captured in the QALY calculation.....	174
3.13	Validation.....	175
3.13.1	Validation of cost-effectiveness analysis	175
3.14	Interpretation and conclusions of economic evidence	176
3.14.1	Summary of evidence.....	176
3.14.2	Relevance and generalisability	177
3.14.3	Strengths of the economic evaluation.....	178

3.14.4 Limitations of the economic evaluation	178
References.....	180

Tables and figures

Table 1. The decision problem	11
Table 2. Technology being evaluated	16
Table 3. Clinical effectiveness evidence: SELECT-GCA	45
Table 4. Summary of SELECT-GCA trial methodology.....	48
Table 5. Baseline patient demographics in SELECT-GCA (FAS1).....	54
Table 6. Baseline patient disease characteristics in SELECT-GCA (FAS1).....	56
Table 7. Patient disposition in SELECT-GCA (FAS1)	59
Table 8. Quality assessment results SELECT-GCA.....	60
Table 9. Proportion of subjects achieving sustained remission at Week 52 (NRI-MI; FAS1)	62
Table 10. Summary of secondary endpoint results (FAS1)	68
Table 11. Summary of TEAEs and deaths in the SS1	76
Table 12. Summary of TEAEs occurring in $\geq 5\%$ of subjects in the SS1 by SOC and PT in any treatment group	77
Table 13. Summary of TEAE leading to discontinuation of study drug reported in $\geq 1\%$ of subjects in the SS1 by PT in any treatment group	79
Table 14. Summary of treatment-emergent AESI in the SS1 by PT.....	82
Table 15. Summary of TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching PBO) occurring in $\geq 5\%$ of subjects in the SS1 by SOC and PT in any treatment group.....	84
Table 16. Summary of TEAEs and deaths in the SS_LT	88
Table 17. Summary of TEAEs occurring $\geq 5\%$ of subjects (PT) in the SS_LT by SOC and PT in any treatment group	90
Table 18. Summary of TEAE leading to discontinuation of study drug reported SS_LT by PT	92
Table 19. Summary of treatment-emergent AESI in the SS_LT by PT	94
Table 20. Summary of TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching PBO) occurring in $\geq 5\%$ subjects in the SS_LT by SOC and PT in any treatment group.....	96
Table 21. Extent of exposure in the SS_LT	98
Table 22. Initial dose of corticosteroid by treatment arms	111
Table 23. Features of the economic analysis	115
Table 24. Intervention and comparator dosing schedules.....	117
Table 25. Health state transitions.....	118
Table 26. AIC for parameter fit on time to first flare.....	120
Table 27. Distributions for base case analysis	122
Table 28. Weekly rate of subsequent flare in each treatment arm	124
Table 29. Model-predicted cumulative flares by treatment arm	124
Table 30. Predicted cumulative corticosteroid exposure.....	129
Table 31. Annual rates of CS-related AE.....	132
Table 32. Probability of CS-related complications.....	134
Table 33. JAKi-related AE rates	135

Table 34. Utilities reported from GiACTA and informing health states for previous GCA appraisals	139
Table 35. Utilities from SELECT-GCA	142
Table 36. Utilities from GiACTA (scenario)	142
Table 37. Disutilities of GCA complications	144
Table 38. Disutilities of CS-related AEs	144
Table 39. Disutilities of JAKi-related AEs	147
Table 40. Drug dosing schedules	148
Table 41. Unit drug costs	148
Table 42. Weekly frequency of treatment monitoring during the treatment period	149
Table 43. Unit costs of monitoring services	149
Table 44. Unit service costs and proportion of patients receiving services in remission state	151
Table 45. Distribution of visit frequency and disease management cost per week in remission state	151
Table 46. Unit service costs and proportion of patients receiving services in flare state	152
Table 47. Distribution of visit frequency and disease management cost per week in flare state	152
Table 48. Costs associated with GCA complications	153
Table 49. CS-related AE costs	154
Table 50. JAKi-related AE costs	156
Table 51. Summary of variables applied in the economic model	158
Table 52. Assumptions in the CEA	161
Table 53. Base-case results	163
Table 54. Net monetary and net health benefit	164
Table 55. PSA inputs	166
Table 56. Probabilistic base-case results (with PAS) – overall population	170
Table 57. Scenario analyses	172

Figure 1. Positioning of upadacitinib in the current treatment pathway	40
Figure 2. SELECT-GCA trial design	48
Figure 3. Proportion of subjects achieving sustained remission at Week 52 (NRI-MI; FAS1)	63
Figure 4. Proportion of subjects achieving sustained complete remission from Week 12 through Week 52 (NRI-MI; FAS1)	64
Figure 5. Cumulative corticosteroid (prednisone/prednisolone equivalent) exposure through Week 52 (AO; FAS1)	65
Figure 6. A) Proportion of subjects who experience at least 1 GCA flare and B) number of GCA flares per subject through Week 52 (AO; FAS1)	66
Figure 7. Time to first flare through Week 52 (FAS1)	67
Figure 8. A. Change from baseline in A) SF-36 PCS and B) FACIT fatigue at Week 52 (MMRM; FAS1)	71
Figure 9. Proportion of subjects achieving sustained remission at Week 52 by subgroup (NRI-MI; FAS1)	73

Figure 10. PRISMA diagram illustrating the study selection process for identifying cost-effectiveness studies for the original SLR (2010 to 10 May 2024).....	109
Figure 11. Model state transition structure.....	115
Figure 12. Parametric extrapolation of TTFF for UPA + 26-week corticosteroid tapering	121
Figure 13. Parametric extrapolation of TTFF for PBO + 52-week corticosteroid tapering	122
Figure 14. Parametric extrapolation of TTFF	123
Figure 15. PRISMA diagram illustrating the study selection process for identifying health-related quality of life studies for the SLR update (searches to 18 February 2025)	138
Figure 16. Cost-effectiveness scatter plot for upadacitinib versus CS	168
Figure 17. Cost-effectiveness acceptability curve for upadacitinib versus CS	169
Figure 18. DSA tornado plot for upadacitinib versus CS	171

Executive summary

Giant cell arteritis (GCA) is a disease with significant unmet need due to disease symptoms and cumulative corticosteroid burden, with patients having limited safe and effective treatment options. Upadacitinib offers a flexible and cost-effective advanced treatment option for patients who currently face life-changing side effects from long term corticosteroid treatment and frequent disease relapses. Upadacitinib's once-daily oral administration and novel mechanism of action compared with current treatments would provide healthcare practitioners with an effective alternative that leads to improved patient outcomes.

Giant cell arteritis

- GCA is a chronic, immune-mediated condition involving the inflammation of the arterial walls, and is the most common form of vasculitis.¹⁻³ An estimated 273 per 100,000 people in the UK over 50 years old are affected by GCA, with the condition disproportionately affecting women and those of Northern European or Scandinavian descent.⁴⁻⁶
- The presentation of GCA is considered a medical emergency due to the risk of permanent blindness and serious, life-threatening complications such as stroke and aortic aneurysm.^{3,7} The burden of GCA is life changing for many patients, and the risk of devastating symptoms leads to a higher prevalence of anxiety and depression amongst these patients.^{8,9}
- Patients with GCA have limited treatment options. Corticosteroids are the main treatment option, initially prescribed at high doses to control symptoms, with the aim to taper the dose to zero over 12–18 months. However, disease relapse is common, requiring an increase in corticosteroid dose.^{2,3} As such, patients risk exposure to repeated high doses, with many patients remaining on steroids long term. This leads to a high cumulative dose, and an increase in the risk of corticosteroid-related adverse events. Many of these adverse events result in long-term comorbidities such as osteoporosis, diabetes, hypertension and heart failure, and have a profound effect on patients' quality of life.⁹⁻¹³
- Use of alternative corticosteroid-sparing therapies is limited due to access restrictions. Off-label treatments are sometimes used, but there is significant uncertainty as to their efficacy.^{2,3,14,15}
- Consequently, there is a substantial unmet need for long-term treatments that are both effective, well-tolerated and corticosteroid-sparing, while providing healthcare practitioners with greater flexibility and additional options for managing patients with GCA.

Upadacitinib

- Upadacitinib is a small molecule, reversible, Janus kinase (JAK) inhibitor that preferentially inhibits JAK1. Upadacitinib has the potential to block multiple pathogenic pathways in GCA, by preventing the signalling of several pro-inflammatory cytokines known to be important in GCA pathogenesis.¹⁶⁻¹⁹
- Upadacitinib is proposed as an oral treatment option for all patients with GCA, administered as a once-daily 15 mg tablet alongside a tapering course of corticosteroids, and may be continued as a monotherapy to maintain steroid-free

remission.^{16,20} As upadacitinib is administered as a once daily oral single tablet, its benefits are achieved through a more convenient and less burdensome mode of administration compared with currently available therapies.

Clinical outcomes with upadacitinib

- Results from the SELECT-GCA clinical trial demonstrated the superior efficacy of upadacitinib 15 mg plus a 26-week corticosteroid taper compared with placebo plus a 52-week corticosteroid taper in patients with GCA.²¹⁻²³
- Upadacitinib demonstrated greater efficacy at inducing sustained remission (absence of GCA signs and symptoms and adherence to the protocol-defined corticosteroid taper regime) at Week 52 in the upadacitinib arm (46.4%) compared with the placebo arm (29.0%).²¹⁻²³
- Upadacitinib also demonstrated a clinically meaningful steroid-sparing effect, significantly reducing the median cumulative corticosteroid exposure (1,615 mg) compared with the placebo arm (2,882 mg) at Week 52.²¹⁻²⁴
- Treatment with upadacitinib effectively prevented flares, reducing the number of patients that experienced at least one flare (34.3% versus 55.6%) and the number of flares per subject (0.4 versus 0.7), and increased the time to first GCA flare compared with the placebo arm (HR 0.57).²¹⁻²³
- Upadacitinib was generally well-tolerated, with a safety profile consistent with the known safety profile of upadacitinib across multiple indications.²¹⁻²³

Cost-effectiveness

- GCA can have devastating comorbidities and side effects from corticosteroid use. Consequently, treating GCA patients has a significant cost and resource impact on the NHS.²⁵ To reflect the significant burden of GCA, the model captures both GCA-related complications and corticosteroid-related adverse events (AEs) with their associated healthcare costs and disutilities.
- A cost-utility analysis using a semi-Markov structure found upadacitinib (with the simple patient access scheme (PAS) discounted price applied) is a cost-effective use of NHS resources in treating all adults with GCA. Upadacitinib was associated with a cost saving of [REDACTED] per patient compared with a 52-week corticosteroid tapering regime, and an incremental gain of [REDACTED] quality-adjusted life years. These findings were consistent across new onset and relapsing GCA subgroups as specified in the final NICE scope.
- The base case analysis was presented as a 2-year treatment duration, however cost-effectiveness was maintained over extended treatment durations, including lifetime treatment. Given the heterogeneity of GCA, this supports a flexible treatment duration guided by disease activity, physician judgement, and patient choice.
- Cost-effectiveness was also demonstrated across all scenario and sensitivity analyses, including variations in flare assumptions, utility values, and variation of selected corticosteroid-related AEs, demonstrating the robustness of findings.

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

1.1 Decision problem

Upadacitinib (RINVOQ®) is anticipated to be indicated for the treatment of [REDACTED]. A type II variation application to extend the therapeutic indication to include GCA was submitted to the Medicines & Healthcare products Regulatory Agency (MHRA) on [REDACTED]. The Committee for Medicinal Products for Human Use (CHMP) gave positive opinion on 27 February 2025 and the type II variation application for the GCA indication was granted by the European Commission on 7 April 2025. The submission covers the technology's full anticipated marketing authorisation for this indication. The decision problem addressed in this submission is compared to that specified in the final scope issued by NICE in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with giant cell arteritis	As per NICE scope	
Intervention	Upadacitinib	As per NICE scope	
Comparator(s)	• Tapering course of corticosteroids • Tocilizumab in combination with a tapering course of corticosteroids, or alone if used after corticosteroids • Methotrexate in combination with a tapering course of corticosteroids	• Tapering course of corticosteroids	The population considered in the submission is adults with GCA. The main treatment option for GCA is a tapering course of steroids.^{2,3} However, due to the chronic, relapsing and remitting nature of GCA,^{11,26} patients can require repeated and long-term treatment.¹⁰⁻¹³ Corticosteroids are considered the appropriate comparator for this appraisal given upadacitinib covers the same patient population and is intended as a flexible long-term treatment option for patients. Following insights from clinical experts, tocilizumab is not considered a relevant comparator for the following reasons: 1. Tocilizumab has a restrictive fixed one-year treatment duration and is recommended in relapsing GCA patients only.²⁷ After treatment, relapse rates are high, and patients are forced to return to back to corticosteroids.²⁸ As such it is considered a short-term treatment, and often further reserved for patients with an increased risk of corticosteroids related AEs. 2. Additionally, clinicians reported that the implementation of the treatment duration restrictions have led to access challenges with tocilizumab, leading to its limited use.

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			The administrative hurdles, including the requirement for Blueteq authorisation and the need for multi-disciplinary team alignment, create barriers in accessing tocilizumab for time-sensitive cases. This situation often leads clinicians to revert to corticosteroid treatment to rapidly manage relapses. These challenges are further echoed in a recent report by the Getting It Right First Time (GIRFT) NHS programme,²⁹ which reported use of tocilizumab as lower than anticipated due to the additional bureaucracy associated with access. Additionally, methotrexate is not considered a relevant comparator for the following reasons: 1. Consultation with clinicians has emphasised the varied use of methotrexate as an adjunctive therapy across UK clinical practice. Methotrexate is used according to clinician discretion due to the lack of available alternate treatments and clinician familiarity with methotrexate, with its benefits uncertain due to limited evidence. 2. Due to uncertainty regarding the effectiveness of methotrexate, it is not regarded as an established treatment option.^{2,3} Evidence is derived from three small, double-blind, placebo-controlled trials, however, meta-analyses of these trials have found contradictory results concerning the effectiveness of methotrexate in GCA.^{15,30-33} Therefore, corticosteroids are deemed the only relevant comparator in UK clinical practice for this submission in the population adult patients with GCA, as supported by clinical expert opinion. This

			comparator is addressed in the company's decision problem and aligns directly with the specification in the NICE scope.
Outcomes	The outcome measures to be considered include: • disease remission • time to relapse after disease remission • cumulative dose of corticosteroids • adverse effects of long-term corticosteroid treatment (including weight gain, osteoporotic fractures, hypertension, cataracts, cardiovascular events, mood disturbance and diabetes mellitus) • morbidity (including vision loss, stroke and aortic aneurysm) • mortality • adverse effects of treatment (including thromboembolism) • health-related quality of life	As per NICE scope	
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	As per NICE scope	

	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 and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • People with newly diagnosed giant cell arteritis • People with relapsing giant cell arteritis • People who have experienced previous corticosteroid toxicity or have pre-existing conditions likely to be exacerbated by corticosteroids • People who have had up to 12 months of tocilizumab • People for whom tocilizumab is unsuitable		The population considered in the company submission are adult patients with GCA, aligned to the anticipated marketing authorisation and the NICE scope. However, for completeness, subgroup analyses in newly diagnosed and relapsing GCA subgroups are provided in the Appendix C. The following subgroups are not considered separately explicitly but rather captured within the defined population of adult patients with GCA. 1. People who are unsuitable to corticosteroids: Consultation with UK clinicians emphasised that patients with prior corticosteroid toxicity will still receive corticosteroids in clinical practice to control disease relapse given the lack of alternative treatment options and risk of serious GCA related complications without treatment. Clinicians did not deem this as a clinically distinct subgroup.

			2. People who have had up to 12 months of tocilizumab & people unsuitable to tocilizumab: Similarly, it is understood that patients who are unsuitable for tocilizumab, or following tocilizumab completion would also receive corticosteroids in clinical practice. This submission provides a relevant comparison to corticosteroids as discussed.

Abbreviations: AE, adverse event; BSR, British Society of Rheumatology; EULAR, European Alliance of Associations for Rheumatology, GCA, giant cell arteritis

1.2 Description of the technology being evaluated

A summary of the mechanism of action, market authorisation status, cost and administration requirements associated with upadacitinib are presented in Table 2. The draft summary of product characteristics (SmPC) is provided in Appendix A.

Table 2. Technology being evaluated

UK approved name and brand name	Upadacitinib (RINVOQ®)
Mechanism of action	Janus Kinases (JAKs) are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, haematopoiesis and immune surveillance. The JAK family of enzymes contains four members: JAK1, JAK2, JAK3, and TYK2, which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation modulates gene expression and cellular function. JAK1 is important in pro-inflammatory cytokine signalling while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function. Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits JAK1 or JAK1/3, over JAK2 and TYK2. The inhibition of JAK1 reduces pro-inflammatory cytokine signalling, including interleukin-6 (IL-6) and interferon-γ (IFN-γ), both implicated in the pathogenesis of GCA.
Marketing authorisation/CE mark status	A type II variation application to extend the therapeutic indications to include the treatment of GCA in adult patients was submitted to the MHRA on [REDACTED]. The submission follows the International Recognition Procedure (IRP). A positive opinion from the CHMP was adopted 27 February 2025, and type II variation application approved on the 7 April 2025 by the European Commission.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The proposed indication for upadacitinib is for [REDACTED]. The draft SmPC is provided in Appendix A. As the MHRA submission is in process a public assessment report (PAR) is not available.
Method of administration and dosage	Oral, 15 mg prolonged-release tablet once-daily (OD)
Additional tests or investigations	No additional testing or investigations are required to determine eligibility for upadacitinib in NHS clinical practice
List price and average cost of a course of treatment	Upadacitinib (RINVOQ®) 15 mg tablets Unit price: £28.77

	Pack of 28 tablets: £805.56 Annual maintenance treatment at 15 mg: £10,508.24 Based upon the chronic nature of GCA, upadacitinib 15 mg OD can be continued as monotherapy following discontinuation of corticosteroids. Treatment continues for as long as patients are responding to treatment. Treatment duration should be guided by disease activity, physician judgement, and patient choice. Estimates are based on patients receiving one tablet per day for 365.25 days per year.
Patient access scheme (if applicable)	Upadacitinib (RINVOQ®) 15 mg tablets Unit price: [REDACTED] Pack of 28 tablets: [REDACTED] Annual maintenance treatment at 15 mg: [REDACTED]

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; GCA, giant cell arteritis; IL-6, interleukin-6; IFN- γ , interferon- γ ; JAK, Janus Kinases; OD, once daily; PAR, public assessment report; SmPC, summary of product characteristics; STAT, signal transducers and activators of transcription; TYK, tyrosine kinase

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

Giant cell arteritis

- Giant cell arteritis (GCA) is a chronic immune-mediated inflammatory condition involving inflammation of the arterial walls of medium to large arteries, and is the most common form of vasculitis.¹⁻³ GCA primarily affects adults over 50 years of age of Northern European or Scandinavian descent, and disproportionately affects women.^{4,5} An estimated 273 per 100,000 people in the UK over 50 year of age are affected by GCA.³⁴
- GCA is a chronic condition that goes through periods of remission, in which active symptoms are controlled, and relapse, the recurrence of active signs and symptoms. These relapses can be minor or major and require treatment with an increased corticosteroid dose. Achieving sustained remission is the aim of treatment for GCA,^{2,3} but is not possible for many patients, with an estimated 50% of patients experiencing relapses.^{11,12,35-37}
- The presentation of GCA is considered a medical emergency as patients are at risk of serious complications.^{3,7} Clinical presentation of GCA is driven by the location of the vessels involved. Cranial GCA primarily affects the temporal and other cranial arteries, while large vessel GCA involves extra-cranial arteries such as the aorta and its branches. These are not distinct subtypes however, and patients can present with cranial GCA, large vessel GCA or both.
- For cranial GCA, the most feared symptom is vision loss, which can develop into permanent blindness without immediate treatment.^{38,39} Patients with large vessel GCA are less responsive to treatment and more likely to experience relapse. These patients are at risk of life-threatening complications such as aortic aneurysm or dissection and stroke, with an increased risk of mortality.^{10,40}
- Patients with GCA have decreased health-related quality of life (HRQoL) due to disease symptoms and cumulative corticosteroid burden. This impacts all aspects of patients' daily lives, with a loss of independence, physical disability, and mental health impacts.^{8,9,41,42}

Current treatment pathway

- GCA is a disease with significant unmet need, and patients have limited treatment options. Corticosteroids are the main treatment option, initially prescribed at high-doses to control symptoms with the aim to taper dose to zero over 12–18 months. However, disease relapse is common, and requires an increase to the last effective corticosteroid dose, or to restart

high dose corticosteroids if the relapse is major, where clinical features of ischaemia or evidence of active aortic inflammation are present.^{2,3} Many patients are not well controlled on no, or low-dose corticosteroids, requiring repeated and long-term treatment.¹⁰⁻¹³ Some patients may never discontinue corticosteroids. This leads to a high cumulative steroid burden, with an increase in the risk of corticosteroid-related adverse events.⁴³

- The burden of cumulative corticosteroid exposure is an important factor for patients with GCA. Corticosteroid-related adverse events substantially impact patients with GCA, potentially leading to long-term comorbidities such as diabetes, osteoporosis, hypertension, and heart failure. These require significant healthcare resource utilisation and have a profound impact on health-related quality of life, leaving patients struggling to cope with the loss of normality and having life-changing effects across all aspects of daily living.^{9,41,42,44,45} These serious side-effects impose additional risks to patients, but are not easily avoided due to the risks of relapse when tapering corticosteroids and the limited treatment options available.^{36,46} As such, steroid-sparing options are needed to reduce the burden to patients.
- Outside of corticosteroids, treatment options are significantly limited. The only available targeted treatment option, tocilizumab, is recommended for use in relapsing or refractory GCA patients only and restricted to a fixed one-year treatment duration. Relapse rates beyond initial treatment are high, forcing patients to cycle back to corticosteroids as their only option.²⁸ Additionally its administration via subcutaneous injection may be seen as an inconvenient and painful mode of administration by patients. Finally, access and administrative challenges have resulted in its limited use in clinical practice.²⁹
- Off-label treatments may be used for the treatment of GCA, however, such use is inconsistent in clinical practice, and is primarily driven by a lack of alternative options.^{2,3} There is significant uncertainty related to their benefits due to limited clinical evidence, and as such they are not considered established treatment options.^{2,3,15}

Unmet need

- The current treatments approved for GCA are limited, subject to restrictions to treatment duration and patient population, or are associated with life-changing treatment-related adverse events, and high relapse rates.^{2,3} Patients are forced to balance the risk of relapses and GCA complications with the risk of corticosteroid adverse events.
- As such there remains a substantial unmet need for additional treatment options for GCA, which was emphasised in the responses to the NICE draft scope by NHS England Specialised Commissioning (NHSE), who stated '*there is enormous unmet need for people with GCA*', and the British Society

of Rheumatology ‘*an area of significant unmet need*’.⁴⁷ Long-term treatments are required that are both effective, well-tolerated and corticosteroid-sparing, while providing healthcare practitioners with greater flexibility and additional options for managing patients with GCA.

Upadacitinib

- Upadacitinib is a small molecule, reversible, Janus kinase (JAK) inhibitor that preferentially inhibits JAK1. Upadacitinib has the potential to block multiple pathogenic pathways in GCA, by preventing the signalling of a number pro-inflammatory cytokines implicated in GCA pathogenesis such as IFN- γ and IL-6 that signal through the JAK/STAT pathway.¹⁷⁻¹⁹
- The proposed positioning for upadacitinib is as a treatment option for adult patients with GCA, aligned with the proposed marketing authorisation. Upadacitinib is recommended alongside a tapering course of corticosteroids, and may be continued as monotherapy following the discontinuation of corticosteroids, with treatment duration guided by disease activity, clinician judgement, and patient choice.⁴⁸ As upadacitinib is administered as a once daily oral single tablet, its benefits are achieved through a more convenient and less burdensome mode of administration compared with currently available therapies.
- Upadacitinib has a novel mechanism of action compared with current treatments, with the potential to be a valuable, flexible, and long-term corticosteroid-sparing treatment option.
- Upadacitinib would provide healthcare practitioners and patients with a much-needed alternative that reduces the need for burdensome corticosteroid treatment and associated long-term adverse events, while improving disease outcomes.

1.3.1 Disease overview

Giant cell arteritis (GCA) is a chronic immune-mediated disease characterised by granulomatous inflammation of the arterial walls in medium to large arteries, leading to vascular remodelling and occlusion.^{17,49,50} It is the most common form of vasculitis, affecting adults aged > 50 years, and disproportionately affects women aged 70–79 years.¹ Clinical presentation of GCA varies depending on the location of blood vessels involved; these may be cranial, extra-cranial or both, with phenotypes commonly overlapping. The typical manifestation of GCA is cranial, and presents with

symptoms such as headaches, scalp tenderness, and jaw claudication.^{1,51,52} One of the most feared complications of cranial GCA is the risk of vision loss due to ischaemia of the ophthalmic artery.^{2,3} GCA may also affect large extra-cranial vessels such as the aorta, which can lead to severe and life-threatening cardiovascular complications such as aortic aneurysm and stroke.^{17,51,53,54} GCA is considered a medical emergency due to the risks of permanent vision loss and severe cardiovascular complications.^{2,3}

Due to a lack of other treatment options, immediate treatment with high-dose corticosteroids is required to minimise risks and induce remission.^{51,53,55,56} Achieving sustained, steroid-free remission is considered the primary goal for the treatment of GCA, however, disease recurrence, known as relapse or a disease flare, are common, often recurring, and are a substantial burden to the patient.^{2,3,7,11,12,57} Most patients achieve remission but experience flares and are considered to have relapsing disease. However, some patients fail to respond adequately to standard treatment and achieve sustained remission and are considered to have refractory disease.

An estimated 50% of patients with GCA experience relapse, often in the first year following diagnosis.^{11,12,35-37} Relapses remain a major concern for patients with GCA, with recurrence of symptoms leading to a reduction in quality of life, and the increased risk of long-term complications and mortality a considerable source of anxiety for patients.^{8,9} Importantly, treatment for relapse involves an increase in corticosteroid doses, often leaving patients on high doses for years, with some never able to safely discontinue the treatment.^{2,3} This long-term exposure to corticosteroids leads to treatment-related adverse events (AEs) that have a cumulative impact on patients and further contribute to the burden of disease and risk of mortality.^{3,11,12,35,36,43,58,59} Corticosteroids have effects throughout the body, leading to a wide range of AEs which can be debilitating, long-term, and life-threatening, including hypertension, type 2 diabetes mellitus, osteoporosis, and heart failure.⁶⁰⁻⁶⁴

Patients with GCA have limited treatment options, and as such often have no choice but to endure these AEs and risks to health.

1.3.1.1 Epidemiology

GCA is the most common form of vasculitis. The condition primarily affects adults > 50 years of age, with risk increasing sharply with age; in a study on a Swedish population, the incidence rate of GCA increased from 2.0 per 100,000 in patients aged 50–60, to 31.3 per 100,000 in those aged 71–80.^{1,65,66}

GCA is most common in Caucasians of Northern European or Scandinavian descent; as such, the incidence varies widely between regions.⁴ In the UK, GCA has an incidence of around 2.2 per 10,000 person-years,⁶⁷ with 94.3% of patients being white British or Irish.⁵ The incidence varies by UK region, with highest incidence in South and East England, and lowest in Scotland.⁶⁷ Incidence also varies according to sex, with females disproportionately affected by GCA; the incidence rate for GCA is reported between 2–3 fold higher in females than in males, and is highest in women aged 70–79 years.^{1,67} Prevalence of GCA follows similar patterns, and a recent report estimated UK prevalence in 2023 at 273 per 100,000 individuals ≥ 50 years.³⁴

1.3.1.2 Clinical presentation

The initial presentation of GCA can be severe and is considered a medical emergency. The exact clinical presentation varies depending on the location of affected arteries. The typical manifestation of GCA is cranial, with up to 80% of patients with GCA presenting with symptoms related to cranial ischaemia. These are commonly severe headaches, temporal artery thickening, loss of pulse, scalp tenderness, jaw claudication, tongue oedema, and more rarely tongue necrosis.^{1,51,52} For cranial GCA, the most feared symptom is permanent vision loss, occurring due to involvement of the ophthalmic artery. Without immediate treatment, this can develop into permanent blindness, a devastating and life-changing condition for patients with

GCA. Studies report around one third of patients with GCA experiencing vision impairment, with permanent vision loss occurring in up to 17%.^{38,49,68}

GCA may also manifest in extra-cranial large vessels such as the aorta, leading to the development of aneurysms or arterial stenosis and presents with limb claudication and aortitis alongside traditional constitutional symptoms including fever, fatigue, night sweats, and weight loss.¹⁰ Large vessel involvement is a considerable and often overlooked problem for patients with GCA. There has been growing awareness of the severity of large vessel involvement in GCA, with these patients less responsive to treatment and approximately nine times more likely to experience multiple relapses.⁴⁰ Serious complications with high mortality risk are associated with large vessel involvement, such as aortic aneurysm or dissection, and stroke. These life-threatening complications represent a substantial burden to patients, impacting their quality of life, and causing significant anxiety and distress due to the associated mortality risks.⁶⁹⁻⁷¹

Large vessel involvement is most accurately diagnosed through the use of imaging techniques such as ultrasonography, magnetic resonance angiography (MRA), computed tomography angiography (CTA), or positron emission tomography (PET).⁷² However, these techniques are not routinely carried out in clinical practice, and as such large vessel involvement in real-world clinical practice may be underdiagnosed.²⁷ As such, large vessel complications often manifest after the initial diagnosis, at a median time of 32 months post diagnosis.^{70,71,73} Research on diagnostic imaging techniques for large vessel involvement has underscored its prevalence, revealing that up to 74% of newly diagnosed GCA patients may exhibit signs of large vessel inflammation.⁷⁴⁻⁷⁶

Considerable overlap exists between GCA and polymyalgia rheumatica (PMR), a related inflammatory disorder that is the most common inflammatory rheumatic disease in people > 50 years old. An estimated 16–21% of patients with PMR have GCA, and PMR is present in 40–60% of patients with GCA.^{46,77,78} These patients are

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more likely to have large vessel involvement; as such, the presence of PMR in patients with GCA increases the risk for relapse and mortality, highlighting these patients as a high-risk population.^{77,79}

The goal of GCA treatment is to induce steroid-free disease remission, however, disease flares or relapses are common, requiring re-initiation of corticosteroid treatment or increasing corticosteroid doses and extending treatment durations. Studies report relapse prevalence in an estimated 50% of patients with GCA.^{11,12,35-37} These relapses can be major or minor. Major relapses are defined by European Alliance of Associations for Rheumatology (EULAR) as recurrence of active disease with clinical features of ischaemia (jaw claudication, visual symptoms, visual loss, scalp necrosis, stroke, or limb claudication) or evidence of active aortic inflammation resulting in aortic dilation, stenosis, or dissection.³ Treatment guidelines recommend that patients with major relapse be treated as if they were new onset, with re-initiation of high-dose corticosteroids.^{2,3} Minor relapses are defined as recurrence of active disease, not fulfilling the criteria for a major relapse.³ Minor relapses are typically treated with dose escalation of corticosteroids to the last effective dose. For patients who relapse after achieving steroid-free remission, the dose of corticosteroid reinitiation is determined at the clinician's discretion, but these lower doses still contribute to the cumulative burden of corticosteroid treatment.^{2,3} Major relapses are serious, and may be considered medical emergencies due to the risk of subsequent organ damage or permanent blindness due to ischaemia.^{3,7}

1.3.1.3 Pathophysiology

GCA is an idiopathic, inflammatory disease associated with a number of genetic and environmental risk factors, with links to infection and autoantigens.^{17,50,55,80} The condition involves a dysregulated immune response to vascular endothelial injury, leading to an autoimmune response, vascular inflammation, and progressive tissue damage.¹⁷ Inflammation of medium and large sized arteries including cranial arteries, the aorta, and arteries emerging from the arch of the aorta is a hallmark of disease,

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with the characteristic formation of granulomas in vessel walls and the formation of multinucleated 'giant cells' giving the disease its name.⁵⁶

The inflammatory cascade involved in GCA is driven by cytokines, signalling molecules that regulate the activity of immune cells and drive inflammatory response. The cascade begins with the activation of dendritic cells in the adventitial layer of the arterial wall. Activated dendritic cells produce chemotactic cytokines that attract T cells and macrophages and produce pro-inflammatory cytokines. These cytokines promote T cell differentiation into T helper (Th1) and Th17 subtypes, producing further cytokines, and activate macrophages to a pro-inflammatory state, perpetuating the inflammatory cycle.^{81,82}

Two key cytokines are involved in GCA: interferon- γ (IFN- γ) and interleukin-6 (IL-6). IFN- γ signalling drives the inappropriate activation of macrophages, leading to vascular damage and production of cytokines such as IL-6.^{83,84} IL-6 is involved in regulating the levels of pro inflammatory Th17 cells and regulatory T cells to maintain immune homeostasis. In GCA, elevated levels of IL-6 dysregulate this balance, contributing towards further unmanaged inflammation.⁸⁵ Importantly, IFN- γ production has been demonstrated to persist despite the corticosteroid treatment, and this underlying inflammation is thought to contribute towards relapse.^{36,81,82}

The effects of both IFN- γ and IL-6 are mediated via the JAK/STAT inflammatory signalling pathway; as such, targeting this pathway has multiple anti-inflammatory benefits. Disrupting this cycle is the basis of JAK inhibitors, used in rheumatoid arthritis and other autoimmune conditions to reduce inflammation.⁸⁶

1.3.1.4 *Diagnosis and assessment of severity*

Due to the potential for irreversible damage to ophthalmic arteries leading to permanent blindness, or potentially fatal large vessel involvement, rapid diagnosis is required for GCA. Despite this, no validated diagnostic criteria exist for GCA; instead, diagnosis is based on a combination of symptom presentation, clinical findings,

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temporal artery biopsy (TAB), laboratory results for inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and diagnostic imaging. An initial diagnosis may be made by general practitioners with referral to secondary care specialists, e.g., ophthalmologists, rheumatologists, or neurologists, for further evaluation and confirmation of the diagnosis.^{2,87} To prevent delays to treatment, confirmation of diagnosis often occurs after treatment with corticosteroids is initiated.^{2,17,87}

The British Society for Rheumatology (BSR) and EULAR treatment guidelines recommend the use of either temporal artery biopsy (TAB) or imaging to confirm diagnosis of GCA.^{2,3} TAB is considered the 'gold standard' diagnostic test for GCA, however, while specificity of TAB is high, sensitivity has been reported as low as 50% in some studies.^{88,89} In addition, for patients with extracranial manifestations of GCA, the use of TAB may result in a false negative. Focus has instead shifted increasingly towards imaging as alternative diagnostic techniques such as ultrasonography, MRA, CTA, and PET which are able to accurately identify large vessel involvement, are less invasive, more sensitive, and crucially, available more quickly than TAB.^{72,90} These imaging techniques however require specialist equipment and training to perform and interpret, limiting their accessibility.⁷² As such, despite guideline recommendations for imaging to detect large vessel involvement,⁷² advanced imaging is not routinely performed within the NHS, particularly during disease monitoring or relapse, or consistently implemented in clinical trials.⁹¹

1.3.1.5 Burden of disease

Clinical and humanistic burden

Corticosteroid related burden

The treatment-related burden of corticosteroids can have a devastating impact on patients with GCA. While guidelines from the BSR and EULAR recommend tapering of corticosteroids over 12–18 months, in clinical practice less than a third of patients with GCA are able to safely discontinue corticosteroids within 2 years of initiation,

Company evidence submission template for upadacitinib for giant cell arteritis [ID6299]

and of those who do discontinue, only 18% of patients are able to do so without occurrence of relapse within 2 years of initiation.⁴⁶ Importantly, some patients never discontinue corticosteroids. NHS England Specialised Commissioning (NHSE) response to the NICE draft scope emphasised the impact corticosteroid-related AEs have on patient quality of life '*(AEs) are primary concerns for patients and have major impacts on quality of life*'.⁴⁷

As such, many patients receive high cumulative doses of corticosteroids, and corticosteroid-related AEs are experienced by up to 83.4% of patients – many of these being permanent, impacting the remainder of the patient's life.⁴⁴ These AEs represent an additional and substantial burden to patients. Corticosteroid-related treatment burden and fears around possible vision loss have been reported to contribute to the feeling of a 'loss of normality' for patients with GCA.⁴² However, shorter duration of corticosteroid tapering is associated with a higher risk of relapse; as such, the burden of corticosteroid-related AEs is a significant concern that cannot currently be avoided.³⁶

The range of corticosteroid-related AEs and side effects is wide. In a US-based retrospective study conducted using IBM Watson Health MarketScan Commercial and Medicare databases, the most commonly experienced events associated with corticosteroid use in GCA over 1 year were osteoporosis (experienced by 22.3% of patients), cataracts (17.6%), opportunistic infections (15.4%), dyspnoea (14.0%), atherosclerosis (10.2%), type 2 diabetes (9.2%), hyperlipidaemia (8.7%), and hypertension (7.9%).⁴⁴ These are serious events that impose additional risks to patients and can have a lifelong impact that is easily underestimated. Notably, the risks for these AEs are linked to cumulative corticosteroid dose; for every 1000 mg increase in exposure, the hazard ratio for AEs increased by 3%.⁴³

As GCA is a chronic condition, patients experience a progressive impact of corticosteroid-related AEs, with specific struggles faced by patients who continue to relapse. Corticosteroid-related AEs have been demonstrated to be one of the three

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factors with greatest negative impact on mental health, with their presence associated with a 10.54 increased odds ratio of moderate-to-severe mental health effects.⁹ The burden associated with cumulative steroid use is a key factor in the patient experience of GCA, and highlights the need for effective steroid-sparing therapies.

Health-related quality of life (HRQoL)

Patients with GCA suffer from substantial reductions in quality of life due to symptoms of the condition and the cumulative burden of corticosteroid treatment, leading to further serious comorbidities.^{41,42,92,93}

Interviews conducted with participants with GCA from the UK and Australia demonstrated that the symptoms of GCA reduce HRQoL by interfering with daily living, introducing functional limitations, negatively affecting psychological wellbeing, and impacting a patient's sense of self. Patients describe GCA as being '*life-changing*' and '*restricting my life totally*'. Symptoms such as fatigue and pain affect the everyday life of patients with GCA, restricting their ability to work, take part in social and leisure activities, or perform household tasks or personal care, one patient stating '*I can't stand up. I haven't got the strength to put my hands up, to hang the washing on the line*'.^{41,42}

These restrictions are substantial; using the SF-12 patient reported survey, 76% of patients with GCA self-report experiencing some form of physical disability, with this being moderate to severe in 46% of patients. Reduced physical autonomy is a major contributing factor to the loss of independence and reduction in quality of life.⁹

For many patients, permanent vision loss is ranked as the most concerning symptom of GCA.⁹² Permanent vision loss is a devastating and life changing symptom experienced by up to 17% of patients, and is associated with feelings of bereavement and vulnerability.^{38,42,49,68} Vision loss has been shown to be significantly associated

with poorer general health, reducing the physical component score using SF-36 survey.³⁹

Notably, the burden of disease often extends beyond the patient, having an impact on family caregivers that is not often assessed in HRQoL studies. Informal caregivers for patients with GCA report considerable disruptions to daily life, resulting in loss of leisure time and income, with a median of 19 hours per week reallocated to activities related to caregiving.⁹⁴

Mental health

GCA is a chronic condition that impacts all aspects of a patient's life, and symptoms can negatively impact patients' mental wellbeing. The chronic nature and serious risks associated with GCA contribute to a higher prevalence of anxiety and depression amongst these patients.^{8,9}

Treatment with corticosteroids places a further burden on patients and is an independent predictor of the presence of anxiety and depression in patients with GCA.^{8,9} A study utilising the HADS patient-reported scoring system demonstrated approximately half of patients with GCA showed signs of possible and a third probable signs of anxiety or depression, respectively.⁸ Similar results are seen using the SF-12 survey, with 33% of patients with GCA self-reporting moderate-to-severe mental impacts due to GCA.⁹ The threat of permanent vision loss is a source of anxiety for patients with GCA, and the presence of permanent vision loss is associated with significantly lower social functioning and mental health.^{9,39,42}

Comorbidities and complications

Patients with GCA present with increased risks for severe comorbidities or complications due to cranial ischaemia, large vessel involvement, or corticosteroid-related AEs.^{1,95,96} Severe complications include myocardial infarction, occurring in approximately 2.4% of GCA patients, or stroke, occurring in 3–7% of patients and a

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leading cause of morbidity and mortality in patients with GCA.^{97,98} Patients with GCA are 1.8 times more likely to experience any cardiovascular event, 4 times more likely to experience a myocardial infarction, and 1.5 times more likely to experience a stroke compared to age-matched controls.^{96,99,100}

This highlights the need for therapies that may control the systemic inflammation and reduce the risk to patients. Large vessel complications may also occur, including aortic aneurysm or dissection, which are serious and potentially deadly.^{70,71,73} Patients with GCA have recently been shown to have an 11–13-fold increased risk of thoracic aortic aneurysm, or 2-fold increased risk of aortic dissection.^{70,96,100-103} These conditions may be further exacerbated by long-term corticosteroid treatment.^{1,43}

Mortality

Patients with GCA are also at increased risk of all-cause mortality, due to a combination of active GCA, comorbidities, and long-term corticosteroid treatment and the associated AEs. The increased risk of all-cause mortality is highest in the first year after diagnosis, and decreases with disease remission and immunosuppressive therapy.^{54,104} In a population-based cohort study conducted in Denmark, all-cause mortality for patients with GCA was demonstrated to be increased by 1.49 fold in the first year after diagnosis compared to the general population, demonstrating the initial high-risk period for patients. Cardiovascular disease was the most common cause of death, increasing the risk of mortality compared to the general population by 1.48 fold, but the presence of GCA also increased the risk of mortality due to infectious disease by 2.58 fold, endocrine disease by 2.67 fold, and gastrointestinal disease by 3.03 fold.¹⁰⁴ Patients who experience severe complications of GCA have further increases to mortality; patients with GCA that experience myocardial infarction have an additional 2.8 times increased mortality compared to patients with GCA without myocardial infarction.¹⁰⁵ Mortality is increased further when large vessels are involved.⁶⁹⁻⁷¹

Economic burden

Management of GCA represents a substantial and long-term healthcare burden due to inpatient, outpatient, and pharmacy requirements.²⁵ This economic burden, particularly due to corticosteroid-related AEs, was emphasised by NHS England Specialised Commissioning (NHSE) in responses to the NICE draft scope '*(GCA) has major cost and resource implications for health care services*'.⁴⁷ In a US study, one third of patients with GCA admitted to the hospital required re-hospitalisation within 6 months, with 20% of patients requiring more than one hospital visit. Patients spend a median of 5 days as an inpatient, with the highest quartile of patients spending 21 days in the hospital per year. These visits represent a burden to both the patient and the healthcare system.⁴⁵

The increased resource use associated with managing GCA translates to a considerable economic burden. In a US-based retrospective study, the costs of treating GCA were estimated at \$6,337 per patient in the first year of diagnosis. Corticosteroid-related AEs were associated with an additional cost of \$7,901 per patient during the first year. In both cases, the majority of costs were due to increased healthcare resource use, including inpatient admissions, outpatient office visits and services, and emergency room visits, rather than pharmacy costs.⁴⁴

Similar results were shown in a retrospective cohort study in France, with healthcare costs associated with treating and managing GCA and treatment related adverse events highest in the first 18 months after diagnosis. Incremental total costs were €4,005 for the first 18 months, €6,406 for the first 3 years, and €7,236 for the first 5 years. The majority of these costs were attributed to healthcare resource use.¹⁰⁶ This illustrates the burden that GCA represents to healthcare systems. Importantly, this healthcare burden is incurred from both the disease and treatment-related AEs, emphasising the unmet need for alternative long-term therapeutic options.

Finally, patients report an impact on their financial circumstances due to additional out-of-pocket costs required for support and disease management. In cases of

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permanent vision loss, additional support from carers or alterations to the home may be needed to cope. Together, GCA and its complications present an additional economic burden to patients.⁴²

1.3.2 Clinical pathway

1.3.2.1 Treatment guidelines

There are currently no NICE guidelines for GCA. Relevant treatment guidelines are published by the BSR and EULAR.^{2,3} The BSR and the EULAR treatment guidelines both emphasise the importance of immediate high-dose corticosteroid therapy (40–60 mg/day) upon suspicion of GCA to prevent complications like permanent visual loss.^{2,3} Both recommend intravenous (IV) methylprednisolone (250/500–1000 mg/day for up to 3 days) in severe cases involving acute visual symptoms but stress not delaying oral corticosteroid treatment if IV therapy is unavailable.^{2,3} While both advocate gradual corticosteroid tapering, BSR suggests a longer tapering period of 12–18 months, whereas EULAR proposes a faster tapering strategy, aiming for ≤ 5 mg/day within 1 year and allowing a 6-month taper to zero when using tocilizumab.^{2,3} Adjunctive therapy with tocilizumab is supported by both as a corticosteroid-sparing option in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of corticosteroid-related AEs or complications).^{2,3} Methotrexate is conditionally recommended by BSR as an adjunctive therapy in patients at high risk of corticosteroid-related AEs or relapsing disease, and EULAR states it may be used as an alternative to tocilizumab.^{2,3}

1.3.2.2 Current management of GCA

The treatment of patients with GCA aims to induce disease remission by suppressing the initial vascular inflammation and to prevent ischaemic end organ damage such as vision loss and stroke. Typically, high dose corticosteroids are required to induce remission.^{2,3} Corticosteroids are the main treatment option, however, long-term use

and high cumulative doses are associated with significant complications, particularly in this predominantly elderly population.^{10,17}

Corticosteroids

Corticosteroids induce rapid symptom relief and reduce the risk of vision loss in patients with GCA.^{10,17} The BSR and EULAR treatment guidelines recommend initial high-dose oral corticosteroids (40–60 mg/day) in patients with new onset disease,^{2,3} although the optimal dose has not been evaluated in clinical trials.⁵³ Patients with acute or intermittent visual loss may initially be given intravenous methylprednisolone (250–1000 mg) daily for up to 3 consecutive days before commencing oral corticosteroid therapy.^{2,3}

Once a patient achieves disease remission corticosteroids are tapered to avoid the associated AEs.^{2,3} The optimal taper schedule has not been established and in clinical practice varies by individual, dependant on response to treatment, risk of relapse, risk of comorbidities, potential for corticosteroid-related AEs, and clinician's discretion.¹⁷ The BSR and EULAR treatment guidelines recommend between 12–18 months taper to a corticosteroid dose $\leq$ 5 mg/day,^{2,3} with EULAR panel members stating that it usually takes about 2 years or more before corticosteroids can be stopped.³

Corticosteroid treatment is associated with high relapse rates.¹⁰ Relapse mainly occurs within the first year of diagnosis, often when corticosteroids are tapered to a low dose, or when tapered too quickly,^{91,107} although the risk remains elevated for years after diagnosis.¹² Observational cohort studies report relapse in 50% of patients treated with corticosteroids, mainly in the first year of treatment.^{11,12,35-37} A meta-analysis reported a 3.3% incidence of major relapse in patients with newly diagnosed or relapsing GCA receiving corticosteroids alone or in combination with corticosteroid-sparing therapy.⁷ Expert opinion from clinicians however has indicated that major relapses may be more common than reported in the literature, estimating that up to 20% of relapses may be major. In the TOC STOP study, a cohort of

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relapsing and refractory GCA patients, relapses were shown to occur in 33% of patients after stopping tocilizumab, with 34% of these being major relapses.²⁸ Patients who are at high relapse risk include women, those with peripheral arthritis, high initial inflammatory markers, and those with evidence of large-vessel involvement.^{53,108,109}

Relapses require an increase in corticosteroid dose and/or slowing of the taper schedule.¹¹⁰ In the event of a major relapse, the BSR and EULAR treatment guidelines recommend restarting high-dose corticosteroids (40-60 mg/day), whereas for a minor relapse, an increase to the previous higher corticosteroid dose is advised.^{2,3} Patients often require repeated and long-term corticosteroid treatment, with studies showing corticosteroid treatment for up to approximately 8 years.¹⁰⁻¹³ This can result in high cumulative steroid doses in GCA patients, with approximately 33% of UK patients receiving doses $\geq 10,000$ mg,¹ subsequently increasing the risk of corticosteroid-related AEs.^{10,24,43,111} The complications of corticosteroid treatment, particularly in elderly patients with GCA, was highlighted by the BSR in responses to the NICE draft scope '*doctors should not be advised to prescribe steroids to older people for lengthy periods because of the well-established side effects*'.⁴⁷

Tocilizumab

Tocilizumab, a monoclonal antibody (mAb) that blocks the IL-6 receptor, is approved by NICE for adults with relapsing or refractory GCA.²⁷ However, clinical expert opinion has highlighted the use of tocilizumab in UK clinical practice is limited for several reasons.

First, tocilizumab is only recommended in a limited group of patients as an adjunctive therapy in refractory or relapsing GCA disease.^{2,3,27} The NICE guidance also stipulates a fixed one-year treatment duration and that patients have not previously received tocilizumab.²⁷ As such it is considered a short-term treatment option for a limited number of patients, and it is often further reserved for patients with a presence or an increased risk of corticosteroid-related AEs. Additionally, following Company evidence submission template for upadacitinib for giant cell arteritis [ID6299]

treatment completion with tocilizumab, relapse rates are high. A UK multicentre observational study (TOC STOP) found that at 6, 12, and 24 months after stopping tocilizumab, 21%, 35%, and 49% of patients respectively had relapsed, requiring an increase in corticosteroids, with 34% of these experiencing a major relapse.²⁸ Due to limited treatment options, these patients return back to corticosteroid management despite the risks.

Second, there are administrative challenges associated with accessing tocilizumab treatment, including the requirement for Blueteq authorisation and the need for multi-disciplinary team alignment, creating barriers to accessing tocilizumab for time-sensitive cases. This situation often leads clinicians to resort to sub-optimal corticosteroid treatment to manage relapses quickly. This is supported by a recent report by the Getting It Right First Time (GIRFT) programme of the NHS, which reported the use of tocilizumab as lower than anticipated due to the additional bureaucracy associated with access.²⁹

Finally, tocilizumab is administered via subcutaneous injection, 162 mg once a week (QW), in combination with a corticosteroid taper.²⁷ This method of administration may further restrict the potential patient population, as patients require training from healthcare professionals, and self-administering injectables may be difficult for some patients, particularly elderly patients or those suffering from physical limitations.²⁰ Additionally, while generally well tolerated, tocilizumab is associated with AEs including gastrointestinal haemorrhage and perforation, infection, headache, hypertension, and injection site reactions.^{112,113}

Consequently, tocilizumab is an underutilised, short-term treatment option for a limited number of patients. This also highlights the substantial unmet need for long-term treatments in a chronic disease like GCA that are effective, well-tolerated, corticosteroid-sparing, and flexible, with treatment durations based on clinical judgement.¹¹⁴

Non-approved treatments

While guidelines may suggest the use of off-label conventional immunosuppressants treatments such as leflunomide and methotrexate as adjunctive therapies, their use in clinical practice is inconsistent. The evidence for these treatments in GCA is limited and uncertain, with treatment used according to clinician discretion due to a lack of treatment options. However, due to the uncertainty regarding their benefits they are not regarded as an established treatment option.^{2,3}

There is limited evidence (predominantly retrospective or case studies) to support the use leflunomide, and it is not recommended in the relevant treatment guidelines.^{2,3}

The evidence base for methotrexate is derived from three small, double-blind, placebo-controlled trials in patients with newly diagnosed GCA, with a low dose of methotrexate (7.5–15 mg/week),³⁰⁻³² with only one trial achieving its primary endpoint.³¹ An individual patient-level meta-analysis of all three trials showed a decrease in disease relapse and reduction in cumulative glucocorticoid exposure in patients treated with methotrexate compared with corticosteroid taper alone.³³

However, a second meta-analysis accounting for heterogeneity between studies did not replicate these findings, demonstrating the uncertainty associated with adjunctive methotrexate use in GCA.¹⁵ There are no published clinical trials that evaluate the higher doses (725 mg/week) of methotrexate.¹¹⁵ As methotrexate is suggested to be considered only in certain populations (refractory or relapsing disease, the presence or an increased risk of corticosteroid-related AEs) as an adjunctive therapy with limited and contradictory supportive clinical evidence, it is not considered an established treatment option. This is supported by NHS England Specialised Commissioning (NHSE) who stated in response to the NICE draft scope '*DMARDs, including methotrexate, do not prevent flares on tocilizumab withdrawal and so should not be considered as an alternative treatment*'.⁴⁷

1.3.3 Unmet need

GCA is a disease area with a significant unmet need.⁴⁷ Current approved treatments are limited and are associated with a profound steroid burden, treatment-related AEs, and high relapse rates.^{2,3}

High-dose corticosteroids are the main treatment option for all patients with GCA.^{2,3} However corticosteroid treatment is associated with high relapse rates (34–80%),^{11,12,35} which require an increase in corticosteroid dose and/or slowing of the taper schedule, with many patients unable to achieve or maintain steroid-free remission and remaining on long-term corticosteroid treatment.¹¹⁰ Several cohort studies report that 40–60% of patients still required corticosteroid treatment over an average follow-up period of 4.8–7.8 years.^{11–13} The substantial cumulative corticosteroid doses experienced by patients are associated with a significant risk of corticosteroid-related AEs, many of which are long-term with a negative impact on quality of life,^{24,42,43} and are associated with increased healthcare cost.⁵⁸

The only targeted treatment, tocilizumab, has a restrictive fixed one-year treatment duration, and is available for relapsing or refractory GCA patients only.²⁷ Additionally the implementation of these restrictions has resulted in access challenges leading to its reduced use in clinical practice. As such it is considered a short-term treatment option, and is often reserved for a limited group of patients with a presence or increased risk of corticosteroid-related AEs (Section 1.3.2.2). Importantly, of the limited patients who receive tocilizumab, a substantial proportion of patients do not achieve remission, or are unable to maintain tocilizumab and corticosteroid-free remission, and remain on long-term corticosteroids.^{28,91,116} NHS England Specialised Commissioning (NHSE) also highlighted in the response to the NICE draft scope '*not all GCA patients respond to or tolerate tocilizumab and so there remains an unmet need for alternative therapies*'.⁴⁷ Additionally, tocilizumab is administered via subcutaneous injection that requires the patient to be trained by a healthcare professional, and for some self-administering injectables may pose additional

physical challenges, particularly in elderly patients or those suffering from physical limitations.²⁰

Patients with GCA who are considered unsuitable for corticosteroid treatment due to comorbidities that may predispose them to steroid-related AEs are a particularly vulnerable population..^{2,3} Clinical expert opinion indicates these steroid-unsuitable patients will often still need to receive low-dose corticosteroids, despite the risks. These patients are at higher risk of relapse, particularly for new onset steroid-unsuitable patients, due to their sub-optimal treatment.

The treatment of GCA presents significant challenges due to disease heterogeneity, high relapse rates, corticosteroid-related AEs, and limited treatment options. There is a substantial unmet need for long-term treatments that are both effective, well-tolerated and corticosteroid-sparing, while providing healthcare practitioners with greater flexibility and additional options for managing patients with GCA. This was emphasised in the responses to the NICE draft scope by NHS England Specialised Commissioning (NHSE), who stated '*there is enormous unmet need for people with GCA*', and the British Society of Rheumatology who commented that GCA was '*an area of significant unmet need*'.⁴⁷

1.3.4 Upadacitinib treatment for giant cell arteritis

1.3.4.1 Mechanism of action

Upadacitinib is a small molecule, reversible JAK inhibitor, engineered to have greater inhibitory potency for JAK1 versus JAK2, JAK3, and TYK2. JAKs are intracellular signalling proteins involved in a wide range of immune and cellular functions, such as cellular proliferation, differentiation, migration, apoptosis and haematopoiesis.⁸⁶

Upadacitinib inhibition of JAK1 reduces pro-inflammatory cytokine signalling, including IL-6 and IFN- γ , both implicated in the pathogenesis of GCA.¹⁷⁻¹⁹

1.3.4.2 *Positioning of upadacitinib*

In line with clinical expert opinion, upadacitinib is anticipated to provide an alternative treatment option for adult patients with GCA; the proposed positioning is indicated in Figure 1. Upadacitinib is recommended in combination with a tapering course of corticosteroids. Upon discontinuation of corticosteroids, monotherapy with upadacitinib should continue, reflecting the importance of managing the chronic nature of GCA. Treatment duration should be tailored based on disease activity, physician judgement, and patient choice. Upadacitinib has a novel mechanism of action compared with current treatments, with the potential to be a valuable, flexible, and long-term corticosteroid-sparing treatment option. Upadacitinib would provide healthcare practitioners and patients with a much-needed alternative that reduces the need for corticosteroid treatment while improving disease outcomes, and addressing the existing gap in effective therapies for patients with GCA.

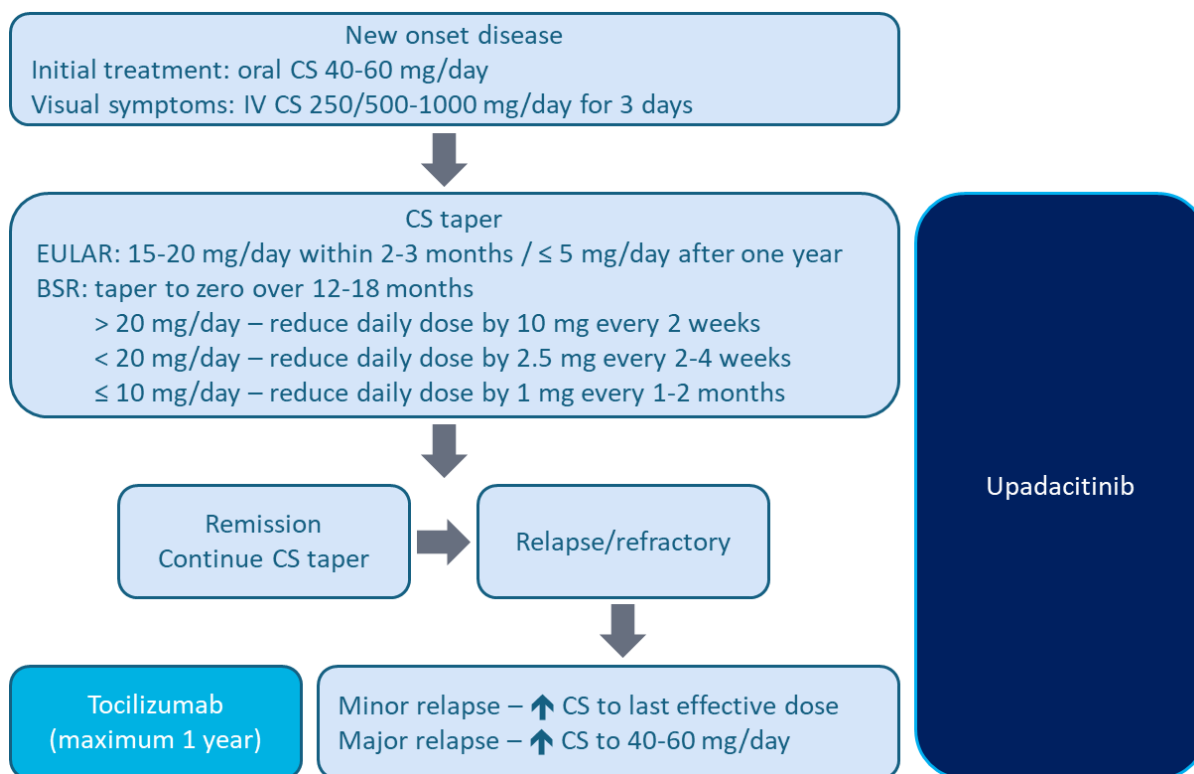


Figure 1. Positioning of upadacitinib in the current treatment pathway

Note: Current treatment pathway based on the BSR and EULAR treatment guidelines and the technology appraisal: tocilizumab for treating giant cell arteritis (TA518)^{2,3,27}

Abbreviations: BSR, British Society for Rheumatology; CS, corticosteroids; EULAR, European League Against Rheumatism; GCA, giant cell arteritis; IV, intravenous

1.4 Equality considerations

The principles that guide the development of NICE guidance and standards include a commitment to reducing health inequalities and supporting strategies that improve population health as a whole, while offering particular benefit to the most disadvantaged.¹¹⁷ There are limited approved treatments for patients with GCA, a disease that disproportionately affects women, and a population that often includes individuals with protected characteristics, such as the elderly and those with potential disabilities, including disease complications like vision loss. Equality issues are a potential concern, as highlighted by clinical consultees in the scoping consultation response.⁴⁷ As such, upadacitinib is a much-needed treatment option to address

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such issues. The use of upadacitinib is not anticipated to raise or worsen any specific equality issues or result in a recommendation that has a negative differential impact on individuals protected by equality legislation, or those with disabilities, compared with the wider population.

2 Clinical effectiveness

Clinical evidence on the efficacy and safety of upadacitinib in patients with GCA comes from SELECT-GCA: a phase 3, randomised, placebo-controlled, multicentre, multinational trial

- The trial enrolled 429 adult (≥ 50 years) subjects with a diagnosis of active GCA. The trial consisted of a 52-week double blind placebo-controlled phase (Period 1) and a 52-week blinded extension (Period 2).²¹⁻²³
- The safety and efficacy of upadacitinib 15mg plus a 26-week corticosteroid taper was compared to placebo plus a 52-week corticosteroid taper in patients with active GCA.
- The SELECT-GCA trial population reflects the target population for upadacitinib in line with the decision problem and were considered by UK clinicians to be generalisable to clinical practice.

Results from the SELECT-GCA trial demonstrate that upadacitinib provides substantial, statistically significant and clinically meaningful improvements in disease control compared to corticosteroids

- A significantly greater proportion of subjects achieved the primary endpoint of sustained remission (defined as absence of GCA signs and symptoms and adherence to the protocol-defined corticosteroid taper regimen) at Week 52 in the upadacitinib 15 mg arm (46.4% [95% CI: 39.6, 53.2]) compared with the placebo arm (29.0% [95% CI: 20.6, 37.5]) ($p = 0.0019$).^{21,23}
- The SELECT-GCA trial also reported several multiplicity-controlled secondary endpoints:
 - A statistically significant greater proportion of subjects sustained complete remission (an absence of GCA signs and symptoms, normalization of ESR to < 30 mm/hour, normalization of high sensitivity CRP (to < 1 mg/dL without elevation [on two consecutive visits] to ≥ 1 mg/dL), and adherence to the protocol-defined corticosteroid taper regimen) from Week 12 through Week 52 in the upadacitinib 15 mg arm (37.1% [95% CI: 30.5, 43.7]) compared with the placebo arm (16.1% [95% CI: 9.3, 22.9]) ($p < 0.0001$).^{21,23}
 - Upadacitinib 15 mg demonstrated a steroid-sparing effect with a statistically significant reduction in median cumulative corticosteroid exposure) through Week 52 (1,615 mg [95% CI: 1,615, 1,635]) compared with the placebo arm (2,882 mg [95% CI: 2,762, 3,253]) ($p < 0.0001$).^{21,23}
 - Upadacitinib 15 mg demonstrated a statistically significant reduction in the proportion of subjects who experience at least one GCA flare through Week 52 (34.3% [95% CI: 27.4, 42.4]) compared with the placebo arm

(55.6% [95% CI: 42.9, 69.2]) ($p = 0.0014$), and a reduction in the number of flares per subject through Week 52 in the upadacitinib 15 mg arm (0.4 [95% CI: 0.3, 0.5]) compared with the placebo arm (0.7 [95% CI: 0.5, 0.9]) ($p = 0.0010$).^{21,23}

- Upadacitinib 15 mg demonstrated a statistically significant increase in time to first GCA flare through Week 52 compared with the placebo arm (hazard ratio 0.57 [95% CI: 0.399, 0.826]) ($p = 0.0025$).^{21,23}
- Treatment with upadacitinib resulted in an improvement in HRQoL. A statistically significant improvement in physical health status was demonstrated by the change from baseline in the SF-36 PCS at Week 52 in the upadacitinib 15 mg arm compared with the placebo arm (least squares (LS) mean: 3.7526 [1.3932, 6.1119]) ($p = 0.0019$).^{21,23} A statistically significant improvement in fatigue was demonstrated by the change from baseline in the FACIT fatigue scale at Week 52 in the upadacitinib 15 mg arm compared with the placebo arm (LS mean: 4.0 [1.33, 6.76]) ($p = 0.0036$).²¹
- The increase in time to first flare and the reduction in the number of flares are key aims for the management of GCA. As such, these secondary outcomes are included in the economic model as discussed in Section 3.3.1.

The safety analysis of SELECT-GCA demonstrated that upadacitinib was generally well-tolerated and the safety profile consistent with the known safety profile derived from randomised clinical trials with over 15,000 patient-years of treatment exposure in multiple indications.^{21,23,118,119}

- Treatment-emergent adverse events (TEAEs) were generally balanced across treatment arms through Week 52 and in the long-term extension (■% of subjects having ■ weeks of exposure to upadacitinib).^{21,23,120} The majority of TEAEs according to the Common Terminology Criteria for Adverse Events (CTCAE) were grade ≤ 2 in severity, and the proportion of TEAEs leading to discontinuation of study drug was similar across both treatment arms.^{21,23,120}
- The proportion of subjects who experienced adverse events of special interest (AESI) was similar between upadacitinib 15 mg and placebo arms through Week 52 and in the long-term extension.^{21,23,120} No cases of adjudicated MACE were reported in the upadacitinib 15 mg arm through Week 52 and in the long-term extension.^{21,23,120} The proportion of subjects who experienced a non-fatal VTE was comparable across treatment arms through Week 52.^{21,23,120} In the long-term extension only one non-fatal event of adjudicated VTE was reported in the upadacitinib 15 mg arm in a subject with multiple risk factors for VTE.^{21,23,120}

Upadacitinib is an efficacious long-term corticosteroid-sparing therapy for patients with GCA

- The main treatment aim of GCA is to induce disease remission by suppressing the initial vascular inflammation and to prevent ischaemic end organ damage such as vision loss and stroke. Upadacitinib is anticipated to provide clear clinical benefits to GCA patients as reflected in the significant and clinically meaningful improvements in driving and maintaining disease control by preventing flares and inducing sustained remission in SELECT-GCA^{21,23}.
- Furthermore, upadacitinib was generally well-tolerated with a safety profile generally consistent with the known safety profile derived from previous randomised clinical trials in multiple indications.^{21,23,118,119}
- The significant reduction in median cumulative steroid dose demonstrates the steroid-sparing benefit of upadacitinib and its potential to reduce corticosteroid-related side effects and improve patients' quality of life.

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was undertaken to identify all the relevant clinical effectiveness (efficacy and safety) evidence relating to interventions for the treatment of GCA. The SLR was conducted in alignment with the CRD's guidance for systematic reviews, the Cochrane Handbook for Systematic Reviews, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and requirements set out by NICE.¹²¹⁻¹²⁴ Full details of the process and methods used to identify and select the relevant clinical evidence are summarised in Appendix B. Database searches were initially conducted in April 2024, with a subsequent update in February 2025. In total 14 reports corresponding to 4 unique trials were considered suitable for inclusion in this review.

2.2 List of relevant clinical effectiveness evidence

Direct clinical evidence is provided for upadacitinib 15 mg plus a 26-week corticosteroid taper versus corticosteroids plus a 52-week corticosteroid taper in the SELECT-GCA phase 3 trial (NCT03725202),¹²⁵ comprising comparative efficacy data

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in the overall adult GCA population (primary analysis; ITT) and sub-populations considered (new-onset and relapsing GCA). The trial evaluated the efficacy and safety of upadacitinib in adult patients ≥ 50 years with active new onset or relapsing GCA.¹²⁵ The trial consisted of a 52-week double blind placebo-controlled phase (Period 1) and a 52-week blinded extension (Period 2).¹²⁵ A summary of the trial details is provided in Table 3. The trial concluded in [REDACTED] and this submission presents the most recent data cutoff for 06 February 2024 and includes all subjects who completed Period 1 and approximately [REDACTED] of subjects who have completed Period 2.

Additional supportive evidence includes the following:

1. A real-world evidence study (RWE) has been undertaken to derive patient characteristics, economic burden, treatment patterns, and burden of corticosteroid-related AEs in patients with GCA. This was a retrospective observational study on the IBM Watson Health MarketScan Commercial and Medicare Supplement.⁴⁴
2. An advisory board has been conducted with UK clinical and health economics experts (February 2025). The purpose was to ensure the company's approach for this submission aligned with clinical and health economic opinion with regards to evidence base, positioning, population, and economic model.

Table 3. Clinical effectiveness evidence: SELECT-GCA

Trial name	SELECT-GCA (NCT03725202)
Study design	A phase 3, randomised, double-blind, placebo-controlled, multicentre trial
Population	Adults ≥ 50 years with active new onset or relapsing GCA
Intervention(s)	Upadacitinib (daily oral tablet) with a 26-week CS taper regimen
Comparator(s)	Placebo with a 52-week CS taper regimen
Indicate if study supports application for marketing authorisation	Yes

Trial name	SELECT-GCA (NCT03725202)
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem (bold indicates outcomes that are incorporated into the model)	Primary endpoint: Sustained remission at Week 52 Secondary endpoints: Sustained complete remission from Week 12 through Week 52 Cumulative CS exposure through Week 52 Time to first disease flare through Week 52 Proportion of subjects who experience at least 1 disease flare through Week 52 Number of disease flares per subject through Week 52 Change from Baseline in the SF-36 at Week 52 Change from Baseline in FACIT-Fatigue at Week 52 Change from Baseline EQ-5D-5L at Week 8, 24, and 52 Rate of CS-related AEs through Week 52
All other reported outcomes	Assessment of TSQM at Week 52 Complete remission at Week 24 and 52 Assessment of PGIC Week 8, 12, 24, and 52 Change from Baseline in PGA at Week 24 and 52 Proportion of subjects with GCA-related Health Resource Utilisation at Week 24 and 52 Proportion of patients in remission through Week 52

Abbreviations: AE, adverse events; CS, corticosteroid; EQ-5D-5L, EuroQoL Five Dimensions Five Levels Questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; GCA, giant cell arteritis; N/A, not applicable; PGA, Patient Global Assessment; PGIC, Patients' Global Impression of Change; SF-36, 36-item Short Form Quality of Life Questionnaire; TSQM, Treatment Satisfaction Questionnaire for Medication

Source: AbbVie data on file SELECT-GCA CSR and statistical analysis plan^{21,126}

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 SELECT-GCA methodology

2.3.1.1 Summary of methodology

SELECT-GCA was a phase 3, randomised, double-blind, placebo-controlled, multicentre, multinational trial.²¹⁻²³ The trial enrolled 429 subjects across 100 sites located in 23 countries in Europe (including the UK), North America, Israel, the

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Russian Federation, and Asia Pacific. The study population consists of adults (≥ 50 years) with a diagnosis of active GCA, either new onset or relapsing disease, within 8 weeks of baseline. Active GCA was defined by the presence of at least one of the following: unequivocal cranial symptoms of GCA, unequivocal symptoms of PMR, or other features judged by the investigator to be consistent with GCA or PMR flares, AND an ESR ≥ 30 mm/hr or CRP ≥ 1 mg/dL. New onset disease was defined as diagnosis of GCA within 8 weeks of baseline. Relapsing disease was defined as active GCA in a subject who has failed at least one attempted corticosteroid taper. For the purposes of this submission, it is assumed this definition captures both relapsing and refractory GCA patients. The objective of Period 1 was to evaluate the efficacy and safety of upadacitinib 7.5 or 15 mg once daily (OD) in combination with a 26-week corticosteroid (CS) taper regimen compared to placebo in combination with a 52-week CS taper regimen in subject with new onset or relapsing GCA, as measured by the proportion of subjects in sustained remission at Week 52. The objective of Period 2 was to evaluate the safety and efficacy of continuing versus withdrawing upadacitinib in maintaining remission in subjects who achieved remission in Period 1.

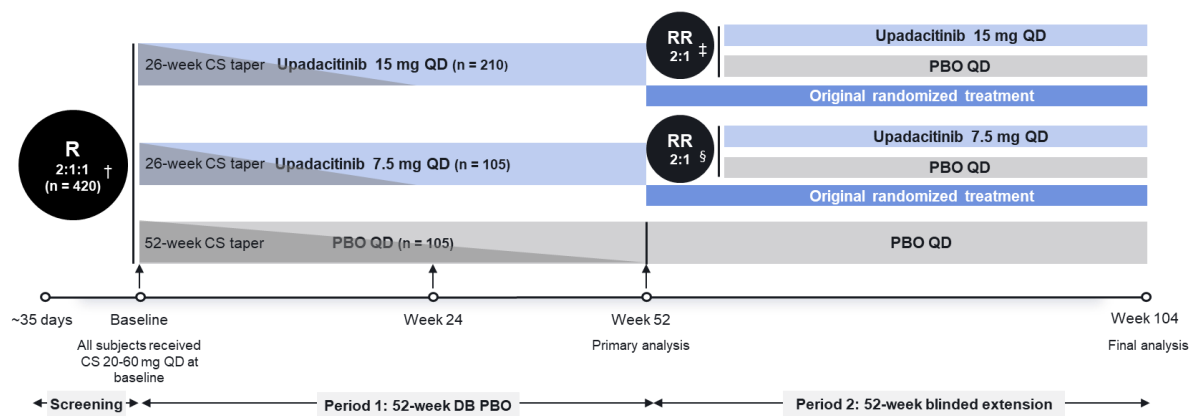
The SELECT-GCA trial design is illustrated in Figure 2 with an overview of the methodology, including the key eligibility criteria, provided in Table 4. Randomisation was performed by interactive response technology (IRT). In Period 1, randomisation of all subjects, except for those in Japan, was stratified by baseline corticosteroid dose (prednisone or prednisolone > 30 mg or ≤ 30 mg), prior use of an IL-6 inhibitor, and whether entering the study with new onset or relapsing disease. In Period 1, subjects were randomised in a 2:1:1 ratio to upadacitinib 15 mg + 26-week corticosteroid taper regimen, upadacitinib 7.5 mg + 26-week corticosteroid taper regimen, or placebo + 52-week corticosteroid taper regimen.

In Period 2, subjects from Period 1 who received upadacitinib and achieved remission for at least 24 weeks prior to Week 52 (end of Period 1) were re-

randomised to either continue upadacitinib or switched to placebo; re-randomisation was stratified by baseline disease status (new onset or relapsing disease). Subjects were re-randomised in a 2:1 ratio to upadacitinib (same dose as Period 1) or placebo. Subjects from Period 1 who received placebo and achieved remission for at least 24 weeks prior to Week 52 continued to receive placebo. Subjects who had an absence of GCA signs and symptoms and were corticosteroid-free but did not meet the above remission criteria continued in Period 2 on their originally randomised treatment. All other subjects discontinued from study drug at the end of Period 1.

Although the SELECT-GCA trial included two doses of upadacitinib, 7.5 and 15 mg, the anticipated market authorisation is for a 15 mg dose in patients with GCA. Therefore, this submission only contains relevant data for the upadacitinib 15 mg dose.

Figure 2. SELECT-GCA trial design



† Stratified by baseline CS dose, prior use of an IL-6 inhibitor (yes, no), and baseline disease status (new onset or relapsing disease)

‡ Subjects who sustained remission for at least 24 consecutive weeks prior to the Week 52 were re-randomised in a 2:1 ratio to upadacitinib or placebo.

§ Subjects who have an absence of GCA signs and symptoms and are CS-free but do not achieve sustained remission for at least 24 consecutive weeks prior to the Week 52 visit continue their originally randomised treatment assignment.

Abbreviations: CS, corticosteroid; DB, double blind; PBO, placebo; QD, every day; R, randomization; RR, rerandomization

Source: AbbVie data on file SELECT-GCA study protocol and clinical study report^{21,22}

Table 4. Summary of SELECT-GCA trial methodology

Trial name	SELECT-GCA (NCT03725202)

Location	100 sites located in 23 countries: Austria, Australia, Belgium, Canada, Czechia, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Japan, the Netherlands, New Zealand, Norway, Portugal, Russian Federation, Spain, Sweden, Switzerland, United Kingdom, United States
Trial design	A phase 3, randomised, double-blind, placebo-controlled, multicentre trial comparing upadacitinib 7.5 or 15 mg + 26-week CS taper regimen, versus placebo + 52-week CS taper regimen
Eligibility criteria for participants	Key eligibility criteria (please refer to the study protocol for a the full list of eligibility criteria):²² • Adult male or female ≥50 years of age • Diagnosis of GCA according to the following criteria: • History of ESR ≥50 mm/hour or hsCRP ≥1.0 mg/dL • Presence of at least either unequivocal cranial symptoms of GCA, or unequivocal symptoms of PMR. • Presence of at least one of either temporal artery biopsy revealing features of GCA, or evidence of large vessel vasculitis by angiography or cross-sectional imaging. • Active GCA, either new onset or relapsing, within 8 weeks of baseline. Active disease is defined by the presence of an ESR ≥ 30 mm/hr or hsCRP/CRP ≥ 1 mg/dL AND at least one of the following: unequivocal cranial symptoms of GCA, unequivocal symptoms of PMR, or other features judged by the investigator to be consistent with GCA or PMR flares. • Subjects must have received treatment with ≥ 40 mg prednisone (or equivalent) at any time prior to baseline and be receiving prednisone (or prednisolone) ≥ 20 mg OD at baseline. • Subjects must have GCA that, in the opinion of the investigator, is clinically stable to allow the subject to safely initiate the protocol-defined CS taper. • Subject must not have any clinically significant medical condition or any other reason which, in the opinion of the investigator, would make the subject an unsuitable candidate to receive study drug or would put the subject at risk by participating in the study.
Trial drugs and method of administration	• Upadacitinib 7.5 and 15 mg oral OD • Placebo (matching upadacitinib) oral OD • There are two phases to the CS (prednisone or prednisolone) taper regimen: - Open-label taper, for CS dosages from 60 mg/day to 20 mg/day - Blinded taper, for CS dosages < 20 mg/day Starting at baseline, all subjects will switch from CS obtained outside of the study to open-label oral prednisone or prednisolone provided by the sponsor at a dose of 20, 30, 40, 50, or 60 mg OD. The initial dose of prednisone or prednisolone will be at the discretion of the investigator, based on disease severity and comorbid medical conditions, but should be at a minimum of 20 mg OD at baseline. Subjects follow the CS taper schedule (refer to study protocol for

	specific details),²¹ completing the open-label phase and transitioning to the blinded phase of taper depending on the CS dose at baseline (i.e., subjects starting on 20 mg/day will transition to the double-blind phase of taper more quickly than patients starting on 60 mg/day). Open-label prednisone or prednisolone will be provided until the dose is tapered to less than 20 mg/day. Subsequently, blinded CS therapy and/or matching CS placebo will be provided for the remaining blinded taper regimen.
Corticosteroid escape therapy	Period 1: - Subjects who require CS escape therapy for their GCA disease will be deemed non-responders in the primary analysis. - Disease flare is defined as an event determined by the investigator to represent recurrence of GCA signs or symptoms or an ESR measurement ≥ 30 mm/hr (attributable to GCA) AND requiring an increase in CS dose. - Subjects who experience disease flare or are unable to adhere to the protocol-defined CS taper regimen during open-label taper of prednisone (at doses of 60 mg/day to 20 mg/day) should switch to receive open-label escape therapy with prednisone or prednisolone at the discretion of the investigator. The subject should continue in the study for the full 52 weeks and receive blinded study drug (upadacitinib or placebo). If, after 2 weeks of open-label CS escape therapy, the investigator believes it is medically necessary to treat the subject with other available treatments, blinded study drug (upadacitinib or placebo) and CS should be discontinued and the subject should be managed based on standard-of-care therapies, which may include tocilizumab. - Subjects who experience disease flare or are unable to adhere to the protocol-defined CS taper regimen during the blinded protocol-defined CS taper should stop the protocol-defined CS taper and receive open-label escape therapy with prednisone or prednisolone starting with at least 20 mg/day at the discretion of the investigator. While on open-label CS escape therapy, the subject should continue in the study for the full 52 weeks and receive blinded study drug (upadacitinib or placebo). If, after 2 weeks of open-label CS escape therapy, the investigator believes it is medically necessary to treat the subject with other available treatments, blinded study drug (upadacitinib or placebo) and CS should be discontinued and the subject should be managed based on standard-of-care therapies, which may include tocilizumab. - Subjects who receive CS escape therapy are eligible to continue in Period 2 (as per randomisation criteria). Period 2: - Disease flare is defined as an event determined by the investigator to represent recurrence of GCA signs or symptoms or an ESR measurement ≥ 30 mm/hr AND requiring initiation of CS. - Subjects who experience disease flare in Period 2 (blinded extension phase) should receive an escape regimen of open-label prednisone or prednisolone at investigator's discretion. Thereafter, open-label escape CS taper will be based on the investigator's

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	judgment and in accordance with local standard-of-care. At the investigator's discretion, these subjects may also discontinue study drug (upadacitinib or placebo and CS) and receive treatment in accordance with local standard-of-care, which may include tocilizumab, and should continue to follow the visit schedule for the remainder of Period 2. • After discontinuation of study drug (upadacitinib or placebo and CS), CS will be prescribed by the investigator, and dosing will be based on the investigator's judgment and in accordance with local standard of care.
Permitted and disallowed concomitant medication	Disallowed: • Subject has not been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or five half-lives (whichever is longer) prior to the first dose of study drug or is not currently enrolled in another interventional clinical study (refer to study protocol for specific details)²¹ • Subject must have no systemic use of known strong cytochrome P450 3A (CYP3A) inhibitors from screening through the end of the study or strong CYP3A inducers 30 days prior to study drug administration through the end of the study • Subject must not have received any live vaccine within 4 weeks (8 weeks for subjects in Japan) prior to the first dose of study drug or expected to need live vaccination during study participation including at least 4 weeks (8 weeks for subjects in Japan) after the last dose of study drug. • Subject must not have had prior exposure to any JAKi (including but not limited to upadacitinib, tofacitinib, ruxolitinib, baricitinib, and filgotinib) • Subject must not have been treated with an IL-6 inhibitor (including but not limited to tocilizumab, sirukumab, and sarilumab) within 4 weeks of baseline. Subjects previously treated with an IL-6 inhibitor must not have experienced disease flare during treatment. • Subject must not have received a biologic or non-biologic DMARD within at least five times the mean terminal elimination half-life of a drug or must follow the specific washout period for the individual drug • Subject must not have chronic use of systemic (oral, intravenous, and/or intramuscular) CS for > 4 years or if ≤ 4 years, an inability, in the opinion of the investigator, to withdraw from CS treatment through the protocol-defined taper regimen • Subject must not have used oral CS for conditions other than GCA within 4 weeks of baseline or intravenous CS within 4 weeks of baseline. Subjects must not have had > 2 courses of systemic CS therapy to treat conditions other than GCA within 1 year prior to baseline • Subject must not have a history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class, or to CS

	- Subject must not have received oral traditional Chinese medicines within 4 weeks prior to baseline Permitted: - Introduction of additional systemic immunosuppressants (such as methotrexate, hydroxychloroquine, cyclosporine, azathioprine, or mycophenolate) concurrent with study drug is prohibited from 4 weeks prior to first dose of study drug through the end of the study. Subjects who discontinue study drug may receive treatment with immunosuppressants in accordance with the investigator's best clinical judgment, irrespective of whether the subject decides to continue participation in the study - Administration of inactivated (non-live) vaccines is permitted prior to or during the study according to local practice guidelines - Inhaled and nasal CS for stable medical conditions are allowed during the study but must have been at a stable dose for ≥ 4 weeks prior to the baseline visit. Short-term use (≤ 10 days) of CS (oral, inhaled, nasal, intravenous, or intramuscular) for non-GCA-related conditions for events such as exacerbation of asthma or chronic obstructive pulmonary disease, allergic reactions, or serious infection when additional CS may be required to prevent adrenal insufficiency (a total of up to 100 mg of prednisone or equivalent through 52 weeks in Period 1 and a total of up to 100 mg of prednisone or equivalent through 52 weeks in Period 2) is allowed during the study - Subjects should be treated with anti-platelet therapy (aspirin or clopidogrel) at the discretion of the investigator and in accordance with local standard-of-care practice - Subjects should receive oral calcium and 25-hydroxy vitamin D supplementation (calcium 1200–1500 mg and vitamin D 8000–1000 IU daily in divided doses), and/or bisphosphonate therapy (e.g., alendronate 70 mg weekly or zoledronate 4 mg annually), unless contraindicated, at the discretion of the investigator and in accordance with local standard-of-care practice for the prevention of glucocorticoid-induced osteoporosis. Study participants with documented osteoporosis should be treated with approved drugs for osteoporosis according to local standard-of-care practice or clinical - During Period 2 of the study, one intra-articular, trigger-point/tender point injection, intra-bursal injection, epidural, or intra-muscular injection is allowed for non-GCA-related conditions if it meets the permitted amount of CS allowed in Period 2
Primary outcome	- Proportion of subjects achieving sustained remission at Week 52. To achieve the endpoint both criteria must be met: - Absence of GCA signs and symptoms from Week 12 through Week 52 - Adherence to the protocol-defined CS taper regimen
Key secondary outcomes	Proportion of subjects achieving sustained complete remission from Week 12 through Week 52 (defined as):

	- An absence of GCA signs from Week 12 through Week 52 - Normalisation of ESR to <30 mm/hour from Week 12 through Week 52 - Normalisation of high sensitivity CRP (to <1 mg/dL without elevation [on two consecutive visits] to ≥1 mg/dL) from Week 12 through Week 52 - Adherence to the protocol-defined CS treatment regimen • Cumulative CS exposure through Week 52 • Time to first GCA flare through Week 52 • Proportion of subjects who experience at least one GCA flare through Week 52 • Rate of CS-related AEs through Week 52 • Change from Baseline in the SF-36 PCS at Week 52 • Change from Baseline in FACIT-Fatigue at Week 52 • Change from Baseline in EQ-5D-5L at Week 8, 24, and 52
Pre-planned subgroup analysis	The primary endpoint was analysed to evaluate the consistency of efficacy between upadacitinib treatment and placebo for the following subgroups: • Sex (Male, Female) • Age group 1 (< 65 years, ≥ 65 years) • Age group 2 (< 65 years, ≥ 65 and < 75 years, ≥ 75 years) • Race group (White, Non-White) • Baseline BMI group (< 25 kg/m², ≥ 25 kg/m² and < 30 kg/m², ≥ 30 kg/m²) • Geographic region group (North America, Western Europe, Eastern Europe, Asia, Oceania) • Nicotine user (Current, Former, Never) • Prior use of IL-6 inhibitor (Yes, No) • New onset of GCA (Yes, No) • Baseline CS dose (> 30 mg, ≤ 30 mg) • Ischemia-related vision loss within 8 Weeks prior to baseline (Yes, No) • History of unequivocal symptoms of PMR without cranial symptoms of GCA (Yes, No)
Duration of study and follow-up	104 weeks (Period 1 52 weeks)

Abbreviations: AE, adverse events; BMI, body mass index; CS, corticosteroid; DMARD, disease modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; EQ-5D, EuroQoL Five Dimensions Five Levels Questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy-Fatigue; GCA, giant cell arteritis; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin 6; JAKi, Janus Kinase inhibitor; OD, once daily; PMR, polymyalgia rheumatica, SF-36, 36-item Short Form Quality of Life Questionnaire
Source: AbbVie data on file SELECT-GCA clinical study report and statistical analysis plan^{21,126}

2.3.1.2 Patient demographics

The baseline patient demographics in the ITT population (FAS1 [all randomised subjects who received at least 1 dose of study drug in period 1]) were generally balanced across the upadacitinib 15 mg and placebo treatment arms (Table 5).^{21,23} Overall, most subjects were female, European, and non-users of nicotine. At baseline the mean age was 70.8 years and 71.6 years; and the mean BMI was 25.27 kg/m² and 25.80 kg/m², in the upadacitinib 15 mg and placebo treatment arms, respectively.

Table 5. Baseline patient demographics in SELECT-GCA (FAS1)

	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 112	N = 209
Age		
n	112	209
Mean (SD)	71.6 (7.33)	70.8 (7.31)
Median	72.0	71.0
Min, Max	52, 87	51, 88
Sex		
Female	77 (68.8)	156 (74.6)
Male	35 (31.3)	53 (25.4)
Race		
White	103 (92.0)	199 (95.2)
Black or African American	2 (1.8)	0
Asian	6 (5.4)	10 (4.8)
Native American Indian or Alaska	0	0
Native Hawaiian or Other Pacific Islander	0	0
Multiple	1 (0.9)	0
Race Group, n (%)		
White	103 (92.0)	199 (95.2)
Non-White	9 (8.0)	10 (4.8)

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Ethnicity, n (%)		
Hispanic or Latino	5 (4.5)	6 (2.9)
Not Hispanic or Latino	107 (95.5)	203 (97.1)
Body Mass Index (kg/m ²)		
N	112	206
Mean (SD)	25.80 (4.32)	25.27 (4.64)
Median	25.12	24.77
Min, Max	16.04, 45.43	11.96, 47.82
Weight (kg)		
N	112	207
Mean (SD)	71.13 (16.03)	68.99 (15.95)
Median	68.00	67.00
Min, Max	37.60, 160.50	35.38, 159.94
Geographic Region, n (%)		
North America	10 (8.9)	9 (4.3)
Western Europe	62 (55.4)	135 (64.6)
Eastern Europe	9 (8.0)	16 (7.7)
Asia	7 (6.3)	10 (4.8)
Japan	5 (4.5)	10 (4.8)
Oceania	24 (21.4)	39 (18.7)
Nicotine User, n (%)		
Current	13 (11.6)	32 (15.3)
Former	33 (29.5)	63 (30.1)
Never	66 (58.9)	111 (53.1)
Unknown	0	3 (1.4)

Note: Percentages calculated on non-missing values

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

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

Source: AbbVie data on file SELECT-GCA clinical study report, Table 4²¹

2.3.1.3 Baseline disease characteristics

Baseline disease characteristics in the ITT population (FAS1) were generally balanced across the upadacitinib 15 mg and placebo treatment arms (Table 6).^{21,23} Most subjects had new onset disease (upadacitinib: 70.8%; placebo 67.9%), a history of unequivocal cranial symptoms of GCA (upadacitinib: 92.8%; placebo 83.9%), evidence of large vessel vasculitis (upadacitinib: 76.1%; placebo 73.0%), and no ischemia-related vision loss (upadacitinib: 90.4%; placebo 80.4%). Approximately, half of subjects had a history of unequivocal symptoms of PMR (upadacitinib: 52.2%; placebo 61.6%). The median disease duration since diagnosis was 41 and 42 days in the upadacitinib 15 mg and placebo treatment arms, respectively. At baseline the mean CRP was 6.720 mg/L and 5.701 mg/L, and the mean ESR was 19.5 mm/hr and 21.7 mg/dL, in the upadacitinib 15 mg and placebo treatment arms, respectively. Most subjects had no history of temporal artery biopsy revealing features of GCA (upadacitinib: 58.9%; placebo 60.7%). The mean corticosteroid dose at baseline was 34.6 mg in both treatment arms, and most subjects had not previously received IL-6 inhibitors (upadacitinib: 95.7%; placebo 93.8%). The mean EQ-5D index value was 0.8143 and 0.8511, in the upadacitinib 15 mg and placebo treatment arms, respectively.

Table 6. Baseline patient disease characteristics in SELECT-GCA (FAS1)

	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 112	N = 209
Prior use of IL-6 inhibitor, n (%)		
Yes	7 (6.3)	9 (4.3)
No	105 (93.8)	200 (95.7)
Baseline disease status, n (%)		
New onset disease	76 (67.9)	148 (70.8)
Relapsing disease	36 (32.1)	61 (29.2)
Baseline CS dose (mg)		

n	112	209
Mean (SD)	34.6 (11.85)	34.6 (12.67)
Median	30.0	30.0
Min, Max	20, 60	20, 60
Baseline CS dose, n (%)		
≤ 30 mg	59 (52.7)	110 (52.6)
> 30 mg	53 (47.3)	99 (47.4)
Disease duration since diagnosis (days)		
n	112	209
Mean (SD)	239.9 (544.89)	222.0 (467.04)
Median	42.0	41.0
Min, Max	15, 2993	14, 2661
Baseline C-reactive protein (mg/L)		
n	112	209
Mean (SD)	5.701 (9.5314)	6.720 (12.7058)
Median	2.250	2.380
Min, Max	0.20, 58.30	0.20, 101.00
Baseline erythrocyte sedimentation rate (mm/hr)		
n	111	209
Mean (SD)	21.7 (25.51)	19.5 (17.46)
Median	12.0	13.0
Min, Max	2, 140	1, 120
Ischemia-related vision loss, n (%)		
Yes	22 (19.6)	20 (9.6)
No	90 (80.4)	189 (90.4)
History of unequivocal cranial symptoms of GCA, n (%)		
Yes	94 (83.9)	194 (92.8)
No	18 (16.1)	15 (7.2)
History of unequivocal symptoms of PMR, n (%)		

Yes	69 (61.6)	109 (52.2)
No	43 (38.4)	100 (47.8)
History of temporal artery biopsy revealing features of GCA, n (%)		
Yes	44 (39.3)	86 (41.1)
No	68 (60.7)	123 (58.9)
Evidence of large vessel vasculitis by angiography or cross-sectional imaging, n (%)		
Yes	81 (73.0)	159 (76.1)
No	30 (27.0)	50 (23.9)
Baseline EQ-5D-5L (index value)		
n	107	198
Mean (SD)	0.8511 (0.1801)	0.8143 (0.1622)
Median	0.8870	0.8590
Min, Max	-0.010, 1.000	0.159, 1.000

Note: Percentages calculated on non-missing values

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

Abbreviations: CS-T, corticosteroid taper; N/A, not applicable; PBO, placebo; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report, Table14.1._5.1²¹

2.3.1.4 Prior and concomitant medication

Overall, prednisone (■■■%) and prednisolone (■■■%) were the most frequently reported prior medication for subjects across the treatment groups followed by acetylsalicylic acid (■■■%), colecalciferol (■■■%), calcium carbonate + colecalciferol (■■■%), omeprazole (■■■%), paracetamol (■■■%), and pantoprazole (■■■%).²¹

All subjects in FAS1 reported use of concomitant medications during the study. Concomitant medication usage was similar across upadacitinib 15mg and placebo treatment arms.²¹

2.3.1.5 Patient disposition

Two hundred and nine subjects received upadacitinib 15 mg and 112 subjects received placebo in Period 1 (Table 7), with 177 (84.7%) and 86 (76.8%) subjects in the upadacitinib 15 mg and placebo arms, respectively, completing Period 1.^{21,23} A

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higher proportion of subjects in the placebo arm discontinued the study compared with the upadacitinib 15 mg arm due to AEs (11.6% versus 8.1%, respectively) and other reasons (4.5% versus 2.4%, respectively) in Period 1.^{21,23} One hundred and fifty-five (74.2%) and 71 (63.4%) subjects in the upadacitinib 15 mg and placebo arms, respectively, completed the study drug in Period 1.^{21,23} A higher proportion of subjects in the placebo arm discontinued the study drug compared with the upadacitinib 15 mg arm due to AEs (20.5% versus 15.3%, respectively) and lack of efficacy (7.1% versus 3.3%, respectively) in Period 1.^{21,23}

Table 7. Patient disposition in SELECT-GCA (FAS1)

	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 112	N = 209
Received randomised study drug, n (%)	112 (100)	209 (100)
Study discontinuation, n (%)		
Completed Period 1	86 (76.8)	177 (84.7)
Ongoing in Period 1	0	0
Discontinued study in Period 1	26 (23.2)	32 (15.3)
Primary reason for study discontinuation, n (%)		
Adverse event	13 (11.6)	17 (8.1)
Withdrew consent	5 (4.5)	10 (4.8)
Lost to follow-up	0	0
COVID-19 infection	0	0
COVID-19 logistical restrictions	1 (0.9)	0
Failure to meet continuation criteria	2 (1.8)	0
Other	5 (4.5)	5 (2.4)
Study drug discontinuation, n (%)		
Completed study drug in Period 1	71 (63.4)	155 (74.2)
Ongoing study drug in Period 1	0	0
Discontinued study drug in Period 1	41 (36.6)	54 (25.8)
Primary reason for discontinuation, n (%)		
Adverse event	23 (20.5)	32 (15.3)
Withdrew consent	3 (2.7)	8 (3.8)

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Lost to follow-up	0	0
Lack of efficacy	8 (7.1)	7 (3.3)
COVID-19 infection	0	0
COVID-19 logistical restrictions	1 (0.9)	0
Other	6 (5.4)	7 (3.3)

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

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

Source: AbbVie data on file SELECT-GCA clinical study report, Table 3²¹

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

A summary of the statistical methodology and analysis set definitions are provided in Appendix L, as informed by the statistical analysis plan.¹²⁶

2.5 Critical appraisal of the relevant clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from SELECT-GCA. The quality assessment for the trial is summarised in Table 8, with the full assessment provided in Appendix B.

Table 8. Quality assessment results SELECT-GCA

Trial number (acronym)	SELECT-GCA (NCT03725202)
Was randomisation carried out appropriately?	Yes – 2:1:1 (period 1) and 2:1 (period 2) randomisation was selected to minimise the number of patients exposed to placebo for an extended period. Randomisation through interactive response technology (IRT) guarded against selection bias. Randomisation in period 1 was stratified by baseline CS dose (prednisone or prednisolone > 30 mg or ≤ 30 mg), prior use of an IL-6 inhibitor, and whether entering the study with new onset or relapsing disease.
Was the concealment of treatment allocation adequate?	Yes – to avoid bias and to ensure the integrity of the blind, all personnel with direct oversight of the conduct and management of the trial (with the exception of the company drug supply management team) were blinded to each subject's

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	treatment until the last subject completes the week 52 visit. Subsequently, the sponsor will be unblinded to period 1 and period 2 study drug assignments to facilitate regulatory filings. The investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, upadacitinib tablets and matching placebo tablets as well as CS capsules provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes – see section 2.3.1.2 and 2.3.1.3
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes – as for the above question ‘was the concealment of treatment allocation adequate?’
Were there any unexpected imbalances in dropouts between groups?	No – see section 2.3.1.5
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – all outcomes that were recorded in the trial have been reported in the CSR, with those outcomes related to the NICE decision problem included in this submission.
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 – the FAS1 (i.e., ITT) population. See section 2.3.1.5 for methods utilised to accounts for missing data.

Abbreviations: CS, corticosteroid; N/A, not applicable

2.6 Clinical effectiveness results of the relevant studies

2.6.1 SELECT-GCA efficacy

The SELECT-GCA trial demonstrated the superiority of upadacitinib 15 mg OD with a 26-week corticosteroid taper versus placebo with a 52-week corticosteroid taper for subjects with GCA with regards to the proportion of subjects who achieved sustained remission and sustained complete remission from Week 12 through Week 52, reduction in cumulative corticosteroid exposure through Week 52, those who experienced at least one GCA flare through Week 52, and the time to first GCA flare through Week 52.^{21,23}

2.6.1.1 Primary endpoint

A statistically significant greater proportion of subjects achieved the primary endpoint of sustained remission (absence of GCA signs and symptoms and adherence to the protocol-defined corticosteroid taper regimen) at Week 52 in the upadacitinib 15 mg arm (46.4% [95% CI: 39.6, 53.2]) compared with the placebo arm (29.0% [95% CI: 20.6, 37.5]), resulting in a placebo-adjusted difference of 17.1% (95% CI: 6.3, 27.8) ($p = 0.0019$) (Table 9 and Figure 3).^{21,23}

Table 9. Proportion of subjects achieving sustained remission at Week 52 (NRI-MI; FAS1)

		PBO + 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
Subjects imputed by MI, n		1	6
Response rate difference compared to placebo	Diff (%)		17.4
	Adj. Diff (%)		17.1
	95% CI‡		6.3, 27.8
	P-value§		0.0019**

Note: PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

† 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 logistic restriction or data after subject received more than 100 mg systemic CS (prednisone or equivalent) for a non-GCA indication. Otherwise, it is based on the normal approximation to the binomial distribution.

‡ § Across the strata, 95% CI for adjusted difference and p-value are calculated according to the Cochran-Mantel-Haenszel test adjusted for strata (Baseline CS dose (prednisone or prednisolone > 30 mg or ≤ 30 mg) and disease status (new onset or relapsing disease)) for the comparison of two treatment groups. Within each stratum, 95% CI for difference are calculated using normal approximation to the binomial distribution. The calculations are based on non-responder imputation incorporating multiple imputation or non-responder imputation only if there are no missing data due to COVID-19 logistic restrictions.

** P-value ≤ 0.01

Abbreviations: CI, confidence interval; CS-T, corticosteroid taper; MI, multiple imputation; PBO, placebo; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report, Table 6^{21,23}

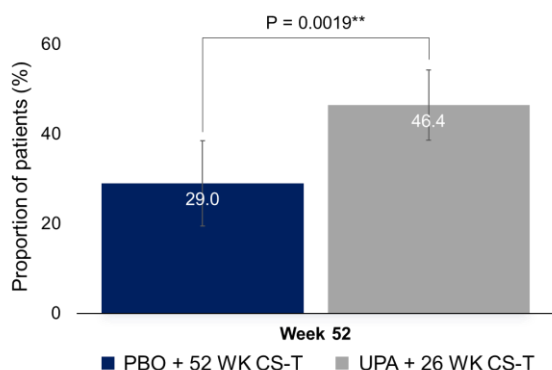


Figure 3. Proportion of subjects achieving sustained remission at Week 52 (NRI-MI; FAS1)

Note: PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

** P-value ≤ 0.01

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

Source: AbbVie data on file SELECT-GCA clinical study report, Table 6^{21,23}

2.6.1.2 Multiplicity-controlled secondary endpoints

Sustained complete remission

A statistically significant greater proportion of subjects achieved the secondary endpoint of sustained complete remission (an absence of GCA signs and symptoms, normalization of ESR to < 30 mm/hour, normalization of high sensitivity CRP (to < 1 mg/dL without elevation [on two consecutive visits] to ≥ 1 mg/dL), and adherence to the protocol-defined corticosteroid taper regimen) from Week 12 through Week 52 in the upadacitinib 15 mg arm (37.1% [95% CI: 30.5, 43.7]) compared with the placebo arm (16.1% [95% CI: 9.3, 22.9]), resulting in a placebo-adjusted difference of 20.7% (95% CI: 11.3, 30.2) ($p < 0.0001$) (Figure 4 and Table 10).^{21,23}

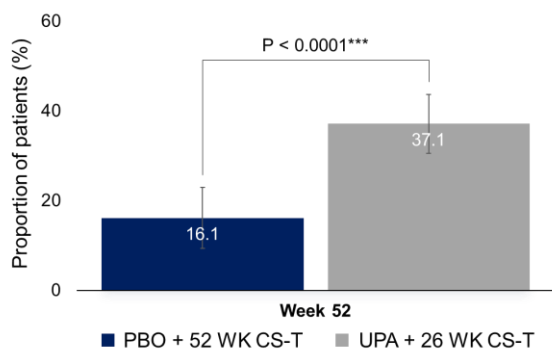


Figure 4. Proportion of subjects achieving sustained complete remission from Week 12 through Week 52 (NRI-MI; FAS1)

Note: PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

*** P-value ≤ 0.001

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

Source: AbbVie data on file SELECT-GCA clinical study report, Table 7^{21,23}

Cumulative corticosteroid exposure

Upadacitinib 15 mg demonstrated a steroid-sparing effect with a statistically significant reduction in median cumulative corticosteroid exposure (prednisone/prednisolone equivalent) (including protocol-defined corticosteroid taper, escape therapy, and corticosteroid treatment for non-GCA indication) through Week 52 (1,615 mg [95% CI: 1,615, 1,635]) compared with the placebo arm (2,882 mg [95% CI: 2,762, 3,253]) ($p < 0.0001$) (Figure 5 and Table 10).^{21,23} Furthermore, the median cumulative additional corticosteroid exposure above protocol-defined corticosteroid taper (due to need for escape therapy or corticosteroid treatment for non-GCA indications) through Week 52 was lower in the upadacitinib 15 mg arm (20 mg [95% CI: 0.0, 40.0]) compared with the placebo arm (512.5 mg [95% CI: 35.0, 1109.0]) (nominal $p < 0.0206$).²¹

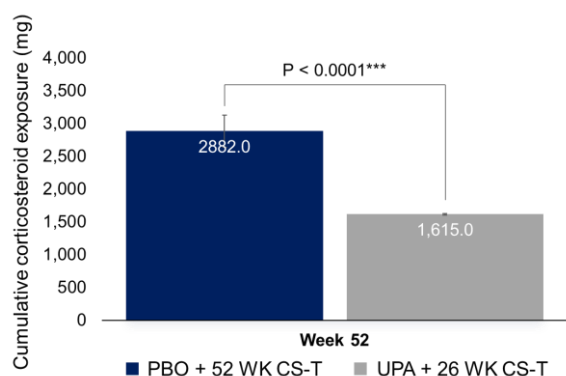


Figure 5. Cumulative corticosteroid (prednisone/prednisolone equivalent) exposure through Week 52 (AO; FAS1)

Note: PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

*** P-value ≤ 0.001

Abbreviations: AO, as observed; CS-T, corticosteroid taper; PBO, placebo; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report, Table 7^{21,23}

GCA flares

Upadacitinib 15 mg demonstrated a statistically significant reduction in the proportion of subjects who experience at least one GCA flare through Week 52 (34.3% [95% CI: 27.4, 42.4]) compared with the placebo arm (55.6% [95% CI: 42.9, 69.2]) ($p = 0.0014$), and a reduction in the number of flares per subject through Week 52 in the upadacitinib 15 mg arm (0.4 [95% CI: 0.3, 0.5]) compared with the placebo arm (0.7 [95% CI: 0.5, 0.9]) ($p = 0.0010$) (Figure 6 and Table 10).^{21,23} A disease flare was defined as an event determined by the investigator to represent recurrence of GCA signs or symptoms or an ESR measurement ≥ 30 mm/hr (attributable to GCA) and requiring an increase in CS dose.²¹ Furthermore, there was a statistically significant increase in time to first GCA flare through Week 52 demonstrated in the upadacitinib 15 mg arm compared with the placebo arm (hazard ratio 0.57 [95% CI: 0.399, 0.826]) ($p = 0.0025$) (Figure 7 and Table 10).^{21,23,120} The increase in time to first flare and the reduction in the number of flares are key aims for the management of GCA. As such, these secondary outcomes are included in the economic model as discussed in Section 3.3.1.

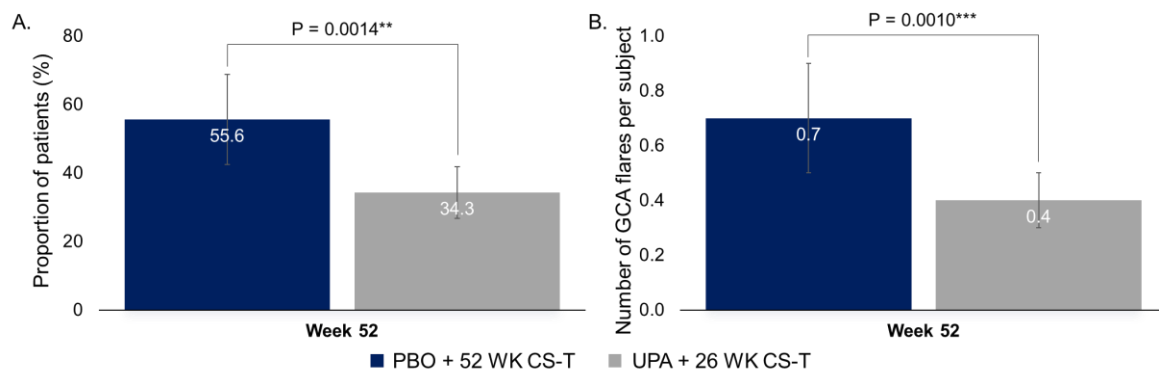


Figure 6. A) Proportion of subjects who experience at least 1 GCA flare and B) number of GCA flares per subject through Week 52 (AO; FAS1)

Note: PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

** P-value ≤ 0.01 , *** P-value ≤ 0.001

Abbreviations: AO, as observed; CS-T, corticosteroid taper; PBO, placebo; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report, Table 7^{21,23}

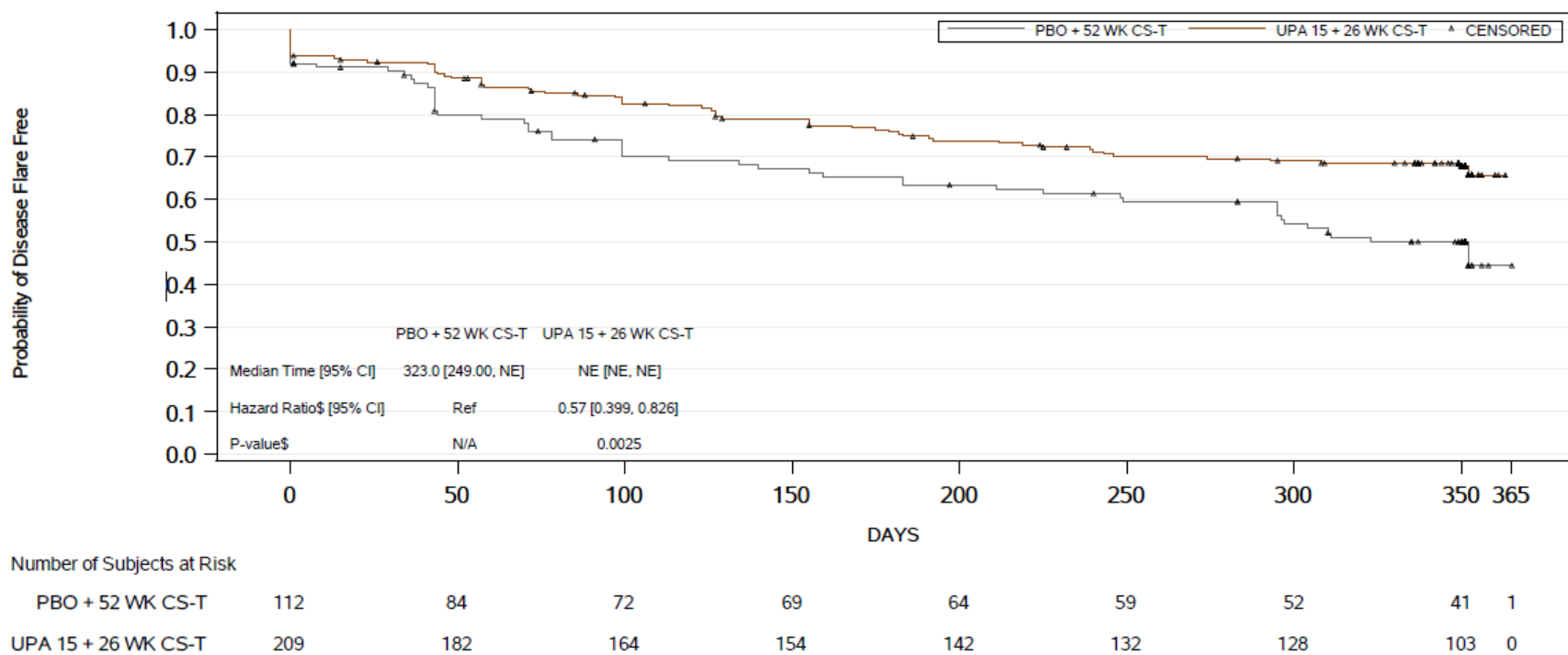


Figure 7. Time to first flare through Week 52 (FAS1)

Note: PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA 15 + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

Hazard ratio is estimated using Cox Proportional Hazard Model

Time (days) is calculated to the first disease flare, from when subjects first meet all three criteria in one assessment: absence of recurrence of GCA signs and symptoms, normalization of ESR, and no CS dose increase. A subject not meeting the criteria for disease flare will be considered having a disease flare at Baseline.

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

Source: AbbVie data on file SELECT-GCA clinical study report appendix, Figure 1¹²⁰

Table 10. Summary of secondary endpoint results (FAS1)

		Within arm	UPA versus PBO	
Endpoint/treatment [†]	N	PE [95% CI]	PE [95% CI] [‡]	P-value [§]
Sustained complete remission from Week 12 through Week 52 (%)				
PBO + 52 WK CS-T	112	16.1 [9.3, 22.9]	20.7 [11.3, 30.2]	< 0.0001***
UPA + 26 WK CS-T	209	37.1 [30.5, 43.7]		
Cumulative CS exposure through Week 52 (mg)				
PBO + 52 WK CS-T	90	2882.0 [2762.00, 3253.00]	N/A	< 0.0001***
UPA + 26 WK CS-T	180	1615.0 [1615.00, 1635.00]		
Time to first GCA flare through Week 52 (days) ^{**}				
PBO + 52 WK CS-T	112	323.0 [249.00, NE]	0.57 [0.399, 0.826] ^ψ	0.0025**
UPA + 26 WK CS-T	209	NE [NE, NE]		
Subjects who experience at least one GCA flare through Week 52 (%)				
PBO + 52 WK CS-T	112	55.6 [42.9, 69.2]	0.47 [0.29, 0.74]	0.0014**
UPA + 26 WK CS-T	209	34.3 [27.4, 42.4]		
Change from baseline in the SF-36 PCS at Week 52				
PBO + 52 WK CS-T	44	-1.2892 [-3.3093, 0.7309]	3.7526 [1.3932, 6.1119]	0.0019**
UPA + 26 WK CS-T	123	2.4634 [1.1707, 3.7561]		
Number of GCA flares per subject through Week 52				
PBO + 52 WK CS-T	112	0.7 [0.5, 0.9]	0.6 [0.4, 0.8]	0.0010***
UPA + 26 WK CS-T	209	0.4 [0.3, 0.5]		
Change from baseline in FACIT-Fatigue at Week 52				
PBO + 52 WK CS-T	45	-2.4 [-4.71, -0.07]	4.0 [1.33, 6.76]	0.0036**
UPA + 26 WK CS-T	123	1.7 [0.18, 3.14]		
Change from baseline in EQ-5D Index score at Week 52				

Company evidence submission template for upadacitinib for giant cell arteritis [ID6299]

PBO + 52 WK CS-T	44	-0.0404 [-0.0832, 0.0024]	0.0537 [0.0036, 0.1038]	0.0356††
UPA + 26 WK CS-T	121	0.0133 [-0.0138, 0.0405]		
Change from baseline in EQ-5D VAS score at Week 52				
PBO + 52 WK CS-T	44	-2.3 [-6.83, 2.24]	6.8 [1.50, 12.12]	0.0121††
UPA + 26 WK CS-T	121	4.5 [1.64, 7.39]		

Note: PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

Within-group estimate: Percentage for categorical endpoints, median for cumulative corticosteroid exposure and time to first GCA flare, least squares mean for continuous endpoints, and mean number of event rate per patient-year for number of GCA flares per subject. Between-group estimate: HR for time to first GCA flare, odds ratio for proportion of subjects who experienced at least 1 GCA flare, difference in least squares means for continuous endpoints, difference in percentages for categorical endpoints.

† Results for categorical endpoints (except for proportion of subjects who experience at least 1 GCA flare) were based on CMH with non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-MI). For SF-36: 68 and FACIT: Patient numbers differ from ITT due to missing assessment and exclusion of data after the intercurrent event of CS escape therapy use.

Number of GCA flares per subject were assessed as events per patient-years based on Poisson model adjusted by stratification factors, with log (duration of study participation in years) as an offset. Robust standard error was used in inference.

Results for continuous endpoints (except for cumulative corticosteroid dose) were based on MMRM. Cumulative corticosteroid exposure was assessed using van Elteren test stratified by stratification factor. Time to first GCA flare was based on KM Method and P-values were based on stratified log-rank test.

‡ Point estimate and 95% CI for treatment difference were based on CMH for categorical endpoints, MMRM for continuous endpoints (except for cumulative corticosteroid exposure), Cox model for time to first GCA flare, and Poisson model for Number of GCA flares per subject.

§ Statistical significance was determined via the graphical multiple testing procedure controlling the overall type I error rate of all primary and secondary endpoints at the 0.05 level.

The Poisson Model is adjusted by stratification factors, with log (duration of study drug exposure in years) as an offset. Robust standard error is used in inference.

ψ Hazard ratio not a point estimate

†† Although this endpoint reached nominal statistical significance, it cannot be formally claimed as such because higher-ranked endpoints in the hierarchical testing were not significant.

‡‡ Time (days) is calculated to the first disease flare, from when subjects first meet all three criteria in one assessment:

absence of recurrence of GCA signs and symptoms, normalization of ESR, and no CS dose increase. If a subject never meets all three criteria in one assessment, the subject will be considered having a disease flare at Baseline.

** P-value ≤ 0.01*** P-value ≤ 0.001

Abbreviations: CI, confidence interval; CS-T, corticosteroid taper; NS, non-significant; PBO, placebo; PE, point estimate; UPA, upadacitinib, VAS, visual analogue scale; WK, week

Source: AbbVie data on file SELECT-GCA clinical study report, Table 7 and 14.2_13.1 and clinical study report appendix, Figure 1^{21,23,120}

2.6.1.3 Patient reported outcomes

The SELECT-GCA trial demonstrated an improvement in HRQoL with upadacitinib 15 mg plus a 26-week corticosteroid taper regimen in subjects with GCA, as measured by the 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS), Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale, and EQ-5D.^{21,23} A statistically significant improvement in physical health status was demonstrated by the change from baseline in the SF-36 PCS at Week 52 in the upadacitinib 15 mg arm compared with the placebo arm (least squares (LS) mean: 3.7526 [1.3932, 6.1119]) ($p = 0.0019$) (Figure 8 and Table 10).^{21,23} A statistically significant improvement in fatigue was demonstrated by the change from baseline in the FACIT fatigue scale at Week 52 in the upadacitinib 15 mg arm compared with the placebo arm (LS mean: 4.0 [1.33, 6.76]) ($p = 0.0036$) (Figure 8 and Table 10).²¹

In general, there was a numerical improvement in HRQoL demonstrated by the change from baseline in EQ-5D Index (LS mean: 0.0537 [0.0036, 0.1038]) (nominal $p = 0.0356$) and EQ-5D Visual Analogue Scale (VAS) (LS mean: 6.8 [1.50, 12.12]) (nominal $p = 0.0121$) scores at Week 52 in the upadacitinib 15 mg arm compared with the placebo arm (Table 10).²¹ Although, the results for EQ-5D Index and VAS scores reached nominal statistical significance, it cannot be formally claimed as such because higher-ranked endpoints in the hierarchical testing were not significant.

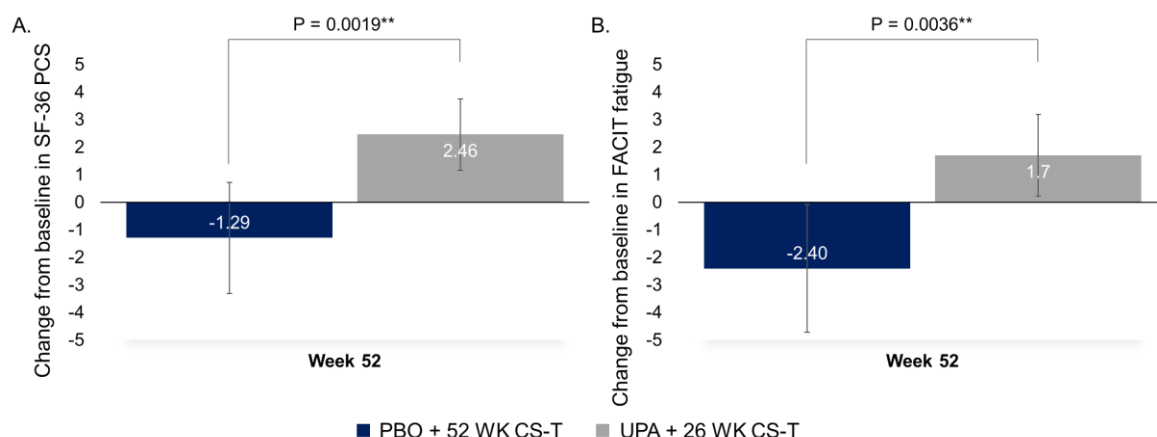


Figure 8. A. Change from baseline in A) SF-36 PCS and B) FACIT fatigue at Week 52 (MMRM; FAS1)

Note: PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

** P-value ≤ 0.01 , *** P-value ≤ 0.001

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

Source: AbbVie data on file SELECT-GCA clinical study report, Table 7^{21,23}

2.7 Subsequent treatments used in the relevant studies

The trial does not include any subsequent treatments. As described in Section 2.3.1.1, subjects who required corticosteroid escape therapy for their GCA disease were deemed as non-responders in the primary analysis. The list of concomitant medication usage is summarised in Section 2.3.1.4.²¹

2.8 Subgroup analysis

SELECT-GCA included a pre-planned subgroup analysis of the primary endpoint across a range of demographic and baseline disease characteristics, including age, sex, race, prior use of IL-6 inhibitors, baseline corticosteroid dose, new onset or relapsing GCA, history of unequivocal symptoms of PMR symptom without cranial symptoms of GCA, and additionally, a post-hoc analysis was performed for subjects with a history of unequivocal symptoms of PMR.^{21,23} The response rates for sustained remission numerically favoured upadacitinib 15 mg compared with placebo across most subgroups, including subgroups based on age, sex, new onset versus relapsing GCA, history of unequivocal symptoms of PMR symptom without cranial symptoms of GCA (Figure 9).^{21,23} The response rates in some subgroups showed

high variability, potentially due to limited sample sizes within those subgroups, e.g., prior use of IL-6 inhibitors.^{21,23}

Subgroups relevant to the NICE decision problem scope include subjects with new onset and relapsing GCA. A post-hoc analysis was also conducted to evaluate the treatment effect upadacitinib 15 mg in the new onset and relapsing GCA subgroups for the following secondary endpoints; sustained complete remission from Week 12 through Week 52, reduction in cumulative corticosteroid exposure through Week 52, those who experienced at least one GCA flare through Week 52, and the time to first GCA flare through Week 52.¹²⁰ Detailed results of the subgroup analysis are found in Appendix C.

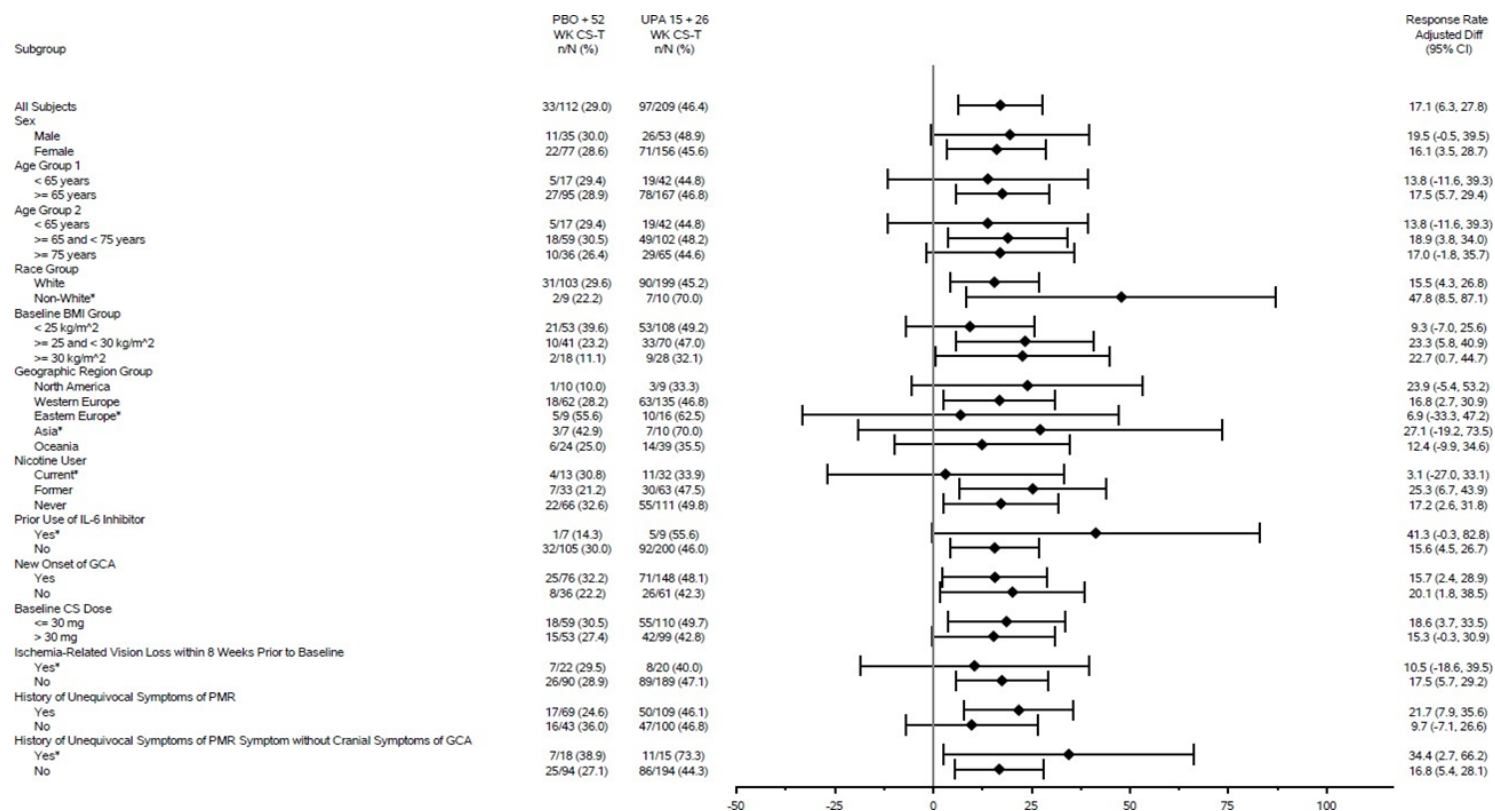


Figure 9. Proportion of subjects achieving sustained remission at Week 52 by subgroup (NRI-MI; FAS1)

Note: PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA 15 + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

95% CI for adjusted difference and P-value were calculated according to the CMH test adjusted for strata (baseline corticosteroid dose [prednisone or prednisolone > 30 mg or ≤ 30 mg] and disease status [new onset or relapsing disease]) for the comparison of 2 treatment groups, with the exceptions: 1) baseline corticosteroid dose was stratified by disease status (new onset or relapsing disease); 2) Disease status was stratified by baseline corticosteroid dose (prednisone or prednisolone > 30 mg or ≤ 30 mg). The calculations were based on non-responder imputation incorporating multiple imputation or non-responder imputation only if there were no missing data due to COVID-19 logistic restrictions.

* Model was not adjusted by stratification factors due to zero subject in a stratum, and 95% CI for difference was calculated using normal approximation to the binomial distribution

Abbreviations: BMI, body mass index; CS, corticosteroid; CS-T, corticosteroid taper; GCA, giant cell arteritis; IL-6, interleukin-6; PBO, placebo; PMR, polymyalgia rheumatica; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report, Figure 2^{21,23}

2.9 Meta-analysis

A network meta-analysis (NMA) was not conducted for this submission, see Section 2.10 for details.

2.10 Indirect and mixed treatment comparisons

Direct clinical evidence is provided for upadacitinib and corticosteroids in SELECT-GCA. As such, indirect treatment comparisons were not required.

2.11 Adverse reactions

The SELECT-GCA trial provides safety data for all subjects who received at least 1 dose of study drug in Period 1 (SS1) (Week 52) and all subjects who received at least one dose of study drug in Period 1 and received the same study drug in Period 2 (SS_LT) (data cutoff date 06 February 2024 [■% of subjects having ■ weeks of exposure to upadacitinib]).^{21,23} All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1, and where applicable report by system organ class (SOC) and preferred term (PT). Data for AEs related to treatment, severity, and deaths is summarised in this section.^{21,23}

2.11.1 Safety analysis set in period 1 (SS1)

2.11.1.1 Summary of treatment emergent adverse events – SS1

Upadacitinib 15 mg was generally well-tolerated through Week 52 (SS1), with a safety profile consistent with the known safety profile derived from randomised clinical trials with over 15,000 patient-years of treatment exposure in multiple indications.^{21,23,118,119}

The proportions of subjects who experienced any treatment emergent AEs (TEAEs) or serious AEs (SAEs) were generally similar between upadacitinib 15 mg arm (96.7% and 23.0%, respectively) and the placebo arm (94.6% and 21.4%, respectively) (Table 11).²¹ The proportion of subjects who experienced TEAEs

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leading to discontinuation of study drug was lower in the upadacitinib 15 mg arm (17.2%) compared with the placebo arm (25.9%) (Table 11).^{21,23}

Treatment emergent AEs accordingly to Common Terminology Criteria for Adverse Events (CTCAE) were predominantly $\leq$ Grade 2 (mild to moderate) in both treatment arms (65.5 – 67.0%) (Table 11).²¹ TEAEs $\geq$ Grade 3 (severe to death) were similar between upadacitinib 15 mg and placebo arms (31.1% and 27.7%, respectively) (Table 11).²¹

The proportion of subjects who experienced TEAEs with reasonable possibility of being related to upadacitinib (or matching placebo), as assessed by the investigator, was 52.6% in the upadacitinib 15 mg arm and 43.8% in the placebo arm (Table 11).²¹ The most common TEAEs considered by the investigator to have a reasonable possibility of being related to upadacitinib (or matching placebo) included worsening of GCA (upadacitinib: 4.8%; placebo: 9.8%) and urinary tract infections (upadacitinib: 4.3%; placebo: 4.5%).²¹

The proportions of subjects who experienced TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching placebo), as assessed by the investigator, was 66.0% in the upadacitinib 15 mg arm and 58.0% in the placebo arm (Table 11);²¹ further details are provided in Appendix L.²¹

Four treatment-emergent deaths were reported; 2 each in the upadacitinib 15 mg arm and placebo arm, and 1 non-treatment-emergent death in the upadacitinib 15 mg arm (Table 11).²¹ In the upadacitinib 15 mg arm one death was attributed to COVID-19 and the other was adjudicated as an unexplained cause. In the placebo arm one death was due to sepsis and the other adjudicated to be due to acute pancreatitis. The non-treatment emergent death in the upadacitinib 15 mg arm was due to stroke that occurred 60 days post study drug discontinuation.^{21,23}

Table 11. Summary of TEAEs and deaths in the SS1

Treatment-emergent events, n (%)	Total population	
	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 112	N = 209
Any treatment-emergent AEs	106 (94.6)	202 (96.7)
AE with reasonable possibility of being related to UPA (or matching PBO)	49 (43.8)	110 (52.6)
AE with reasonable possibility of being related to prednisone/prednisolone (or matching PBO)	65 (58.0)	138 (66.0)
AE by CTCAE Grade		
Grade 1	18 (16.1)	22 (10.5)
Grade 2	57 (50.9)	115 (55.0)
Grade 3	27 (24.1)	55 (26.3)
Grade 4	2 (1.8)	8 (3.8)
Grade 5	2 (1.8)	2 (1.0)
Serious AE	24 (21.4)	48 (23.0)
AE leading to withdrawal of UPA (or matching PBO)	29 (25.9)	36 (17.2)
COVID-19 related AE	12 (10.7)	30 (14.4)
AE results in death	2 (1.8)	2 (1.0)
All deaths	2 (1.8)	3 (1.4)
Occurring ≤ 30 days after last dose of study drug	2 (1.8)	2 (1.0)
COVID-19 related	0	1 (0.5)
Occurring > 30 days after last dose of study drug	0	1 (0.5)
COVID-19 related	0	0

Notes: TEAEs in period 1 (SS1) are defined as any AE with an onset or worsening in severity date on or after the first dose date of study drug and prior to the first dose of study drug in period 2 or no more than 30 days after the last dose of study drug in period 1, whichever occurred firstly.

Subjects are counted once in each row, regardless of the number of events they may have experienced.

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; CS-T, corticosteroid taper; PBO, placebo; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report, Table 14.3._1.1.1.1^{21,23}

The most common TEAEs ($\geq 5\%$ of subjects in any treatment arm) included worsening of GCA (upadacitinib: 23.0%; placebo: 31.3%), headache (upadacitinib: 16.3%; placebo: 11.6%), hypertension (upadacitinib: 13.4%; placebo: 11.6%), COVID-19 (upadacitinib: 13.4%; placebo: 10.7%), arthralgia (upadacitinib: 13.9%; placebo: 13.4%), urinary tract infection (upadacitinib: 10.0%; placebo: 16.1%), back pain (upadacitinib: 12.0%; placebo: 13.4%), nasopharyngitis (upadacitinib: 8.6%; placebo: 11.6%), and diarrhoea (upadacitinib: 8.6%; placebo: 10.7%) (Table 12).

Table 12. Summary of TEAEs occurring in $\geq 5\%$ of subjects in the SS1 by SOC and PT in any treatment group

Treatment-emergent events, n (%)	Total population	
	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 112	N = 209
Any AE	106 (94.6)	202 (96.7)
Eye disorders	22 (19.6)	56 (26.8)
Cataract	2 (1.8)	10 (4.8)
Gastrointestinal disorders	37 (33.0)	93 (44.5)
Abdominal pain upper	5 (4.5)	11 (5.3)
Constipation	2 (1.8)	11 (5.3)
Diarrhoea	12 (10.7)	18 (8.6)
Nausea	4 (3.6)	11 (5.3)
General disorders and administration site conditions	21 (18.8)	73 (34.9)
Fatigue	6 (5.4)	19 (9.1)
Oedema peripheral	3 (2.7)	16 (7.7)
Infections and infestations	66 (58.9)	132 (63.2)
COVID-19	12 (10.7)	28 (13.4)
Cystitis	3 (2.7)	15 (7.2)
Nasopharyngitis	13 (11.6)	18 (8.6)
Upper respiratory tract infection	8 (7.1)	11 (5.3)
Urinary tract infection	18 (16.1)	21 (10.0)

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Investigations	19 (17.0)	35 (16.7)
Weight increased	4 (3.6)	6 (2.9)
Musculoskeletal and connective tissue disorders	56 (50.0)	108 (51.7)
Arthralgia	15 (13.4)	29 (13.9)
Back pain	15 (13.4)	25 (12.0)
Muscle spasms	8 (7.1)	13 (6.2)
Myalgia	5 (4.5)	9 (4.3)
Neck pain	6 (5.4)	3 (1.4)
Osteoarthritis	5 (4.5)	13 (6.2)
Pain in extremity	6 (5.4)	15 (7.2)
Nervous system disorders	32 (28.6)	81 (38.8)
Dizziness	6 (5.4)	10 (4.8)
Headache	13 (11.6)	34 (16.3)
Respiratory, thoracic and mediastinal disorders	14 (12.5)	49 (23.4)
Cough	4 (3.6)	14 (6.7)
Skin and subcutaneous tissue disorders	26 (23.2)	57 (27.3)
Rash	3 (2.7)	11 (5.3)
Vascular disorders	47 (42.0)	83 (39.7)
Giant cell arteritis	35 (31.3)	48 (23.0)
Hypertension	13 (11.6)	28 (13.4)

Notes: TEAEs in period 1 (SS1) are defined as any AE with an onset or worsening in severity date on or after the first dose date of study drug and prior to the first dose of study drug in period 2 or no more than 30 days after the last dose of study drug in period 1, whichever occurred firstly.

Subjects were counted once in each row, regardless of the number of events they may have experienced.

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

Abbreviations: CS-T, corticosteroid taper; PBO, placebo; PT, preferred term; SOC, system, organ, class; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report, Table 12²¹

2.11.1.2 Treatment emergent adverse events leading to discontinuation of study drug – SS1

The proportion of subjects experiencing TEAEs leading to study drug discontinuation was 17.2% in the upadacitinib 15 mg and 25.9% in the placebo arm through Week 52 (SS1) (Table 13).^{21,23} The worsening of GCA was the most frequent TEAE leading to study drug discontinuation in either treatment arm, and was higher in the placebo arm (■%) compared with the upadacitinib 15 mg arm (■%).

Table 13. Summary of TEAE leading to discontinuation of study drug reported in ≥ 1% of subjects in the SS1 by PT in any treatment group

Treatment-emergent events, n (%)	Total population	
	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 112	N = 209
Any adverse event	29 (25.9)	36 (17.2)
Deep vein thrombosis	■	■
Giant cell arteritis	■	■
Pneumonia	■	■
Polymyalgia rheumatica	■	■
Pulmonary embolism	■	■
Substance-induced psychotic disorder	■	■

Notes: TEAEs in period 1 (SS1) are defined as any AE with an onset or worsening in severity date on or after the first dose date of study drug and prior to the first dose of study drug in period 2 or no more than 30 days after the last dose of study drug in period 1, whichever occurred firstly.

Subjects were counted once in each row, regardless of the number of events they may have experienced.

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

Abbreviations: CS-T, corticosteroid taper; PBO, placebo; PT, preferred term; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report, Table 17²¹

2.11.1.3 Adverse events of special interest – SS1

Adverse events of special interest (AESIs) were identified based on upadacitinib findings across all indications and safety concerns reported for other JAK inhibitors.²¹ These included serious infection, opportunistic infection (excluding tuberculosis [TB])

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and herpes zoster), herpes zoster, active TB, malignancy (all types), hepatic disorders, adjudicated GI perforation, anaemia, neutropenia, lymphopenia, creatine phosphokinase elevation, renal dysfunction, adjudicated major adverse cardiovascular events (MACE), and adjudicated embolic and thrombotic events (non-cardiac, non-CNS) events.

The proportion of subjects who experienced AESIs was similar between upadacitinib 15 mg and placebo arms through Week 52 (SS1) (Table 14).^{21,23} No AESIs of active TB, lymphoma, or adjudicated gastrointestinal perforation were reported in either treatment arm.

The proportion of subjects who experienced AESI of serious infections was 5.7% in the upadacitinib 15 mg arm and 10.7% in the placebo arm, respectively (Table 14).^{21,23} No more than 1 subject (by PT) reported an event of serious infection for either treatment arm, except for pneumonia (5 events in the placebo arm), COVID-19 pneumonia, and ophthalmic herpes zoster (2 events each in the upadacitinib 15 mg arm). Most events of serious infections did not lead to discontinuation of the study drug. Two events of serious infections (sepsis in the placebo arm and COVID-19 in the upadacitinib 15 mg arm) resulted in death.

Adverse event of special interest of opportunistic infection occurred in 1.9% and 0.9% of subjects in the upadacitinib 15 mg and placebo arms, respectively (Table 14).^{21,23} These events included oral fungal infection (2 events), oesophageal candidiasis and *Pneumocysts jiroveci* pneumonia (1 events each) in the upadacitinib 15 mg arm; and oesophageal candidiasis (1 event) in the placebo arm. The event of *Pneumocysts jiroveci* pneumonia was serious, severe, and led to discontinuation of study drug. All other events were mild or moderate in severity, and none led to discontinuation of the study drug.

Two events herpes zoster ophthalmicus were reported in subjects who received upadacitinib 15 mg, these were serious, severe, with one leading to discontinuation

of the study drug.^{21,23} All other events of herpes zoster were mild or moderate in severity. Most events were localised to a single dermatome, and there were no events involving the central nervous system. All subjects with herpes zoster fully recovered. Among the subjects who had an event of herpes zoster, the majority did not have a herpes zoster vaccination prior to baseline or history of previous herpes zoster infection.

The proportion of subjects who experienced AESI of malignancy was 4.3% in the upadacitinib 15 mg arm and 2.7% in the placebo arm (Table 14).^{21,23} Nonmelanoma skin cancer (NMSC) events included squamous cell carcinoma (3 events in the upadacitinib 15 mg arm) and basal cell carcinoma (2 events each in the upadacitinib 15 mg and placebo arms). No events of NMSC led to discontinuation of the study drug. Malignancies excluding NMSC were as follows; 1 event each with lentigo maligna, malignant neoplasm of ampulla of Vater, squamous cell carcinoma of the lung, and tongue neoplasm malignant stage unspecified in the upadacitinib 15 mg arm, and 1 event each with prostate cancer and metastatic tonsil cancer in the placebo arm. All events of malignancy resulted in discontinuation of the study drug except for lentigo maligna.

The proportion of subjects who experienced AESI of anaemia was 6.7% in the upadacitinib 15 mg arm and 2.7% in the placebo arm, these were mild in severity and did not lead to discontinuation of the study drug (Table 14).^{21,23} No AESIs of neutropenia were reported in the upadacitinib 15 mg arm, with one reported in the placebo arm.^{21,23} Lymphopenia was only reported in the upadacitinib 15 mg arm (1.4); these were non-serious, mild or moderate, and resolved without discontinuation of the study drug.^{21,23}

Adverse event of special interest of creatine kinase elevations were only reported in the upadacitinib 15 mg arm (2.9%); these were non-serious, mild or moderate, and did not result in discontinuation of the study drug (Table 14).^{21,23} No patients with elevated creatine kinase experienced rhabdomyolysis or myopathy.

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No AESIs of adjudicated MACE were reported in the upadacitinib 15 mg arm, with two (1.8%) (cerebrovascular accident and myocardial ischemia) reported in separate subjects in the placebo arm, with each patient having at least 1 cardiovascular risk factor (Table 14).^{21,23} The cerebrovascular accident was serious, moderate, and led to discontinuation of the study drug. The event of myocardial ischemia was serious, severe, but did not lead to discontinuation of the study drug.

The proportion of subjects who experienced AESI of adjudicated venous thromboembolic events (VTE) was 3.3% in the upadacitinib 15 mg arm and 3.6% in the placebo arm (Table 14).^{21,23} The subjects in the upadacitinib 15 mg arm had at least 1 risk factor for VTE, including previous medical history of thrombosis, smoking, hypertension, obesity, and diagnosis of GCA. All events of adjudicated VTE were non-fatal, however, most were serious, severe, and resulted in discontinuation of study drug.

The short duration of the trial (Period 1 – 52-weeks) and the potential for increased cardiovascular risk in patients with GCA highlights the need for long-term safety assessments. The 52-week blinded extension (Period 2) period of the trial will provide additional data on the safety of upadacitinib through 2 years.

Table 14. Summary of treatment-emergent AESI in the SS1 by PT

Treatment-emergent events, n (%)	Total population	
	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 112	N = 209
Serious infections	12 (10.7)	12 (5.7)
Opportunistic infection excluding TB and herpes zoster	1 (0.9)	4 (1.9)
Herpes zoster	3 (2.7)	11 (5.3)
Malignancy	3 (2.7)	9 (4.3)
Non-melanoma skin cancer (NMSC)	2 (1.8)	5 (2.4)
Malignancy excluding NMSC	2 (1.8)	4 (1.9)

Adjudicated MACE	2 (1.8)	0
Anaemia	3 (2.7)	14 (6.7)
Neutropenia	1 (0.9)	0
Lymphopenia	0	3 (1.4)
Renal dysfunction	3 (2.7)	4 (1.9)
Hepatic disorder	5 (4.5)	11 (5.3)
Creatine phosphokinase elevation	0	6 (2.9)
Adjudicated embolic and thrombotic events (non-cardiac, non-CNS)	4 (3.6)	8 (3.8)
Venous thromboembolic events	4 (3.6)	7 (3.3)
Arterial thromboembolic events	0	2 (1.0)

Notes: TEAEs in period 1 (SS1) are defined as any AE with an onset or worsening in severity date on or after the first dose date of study drug and prior to the first dose of study drug in period 2 or no more than 30 days after the last dose of study drug in period 1, whichever occurred firstly.

Subjects are counted once in each row, regardless of the number of events they may have experienced.

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

† MACE was defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

‡ VTE included deep vein thrombosis and pulmonary embolism (fatal and non-fatal).

Abbreviations: CS-T, corticosteroid taper; PBO, placebo; PT, preferred term; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report, Table 14.3_1.3.1.1^{21,23}

2.11.1.4 Corticosteroid-related adverse events – SS1

Treatment emergent adverse events with reasonable possibility of being related to prednisone/prednisolone (or matching placebo) were investigator assessed. The following definitions were used to assess the relationship of the TEAE to prednisone/prednisolone (or matching placebo):^{21,22}

- Reasonable possibility – after consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
- No reasonable possibility – after consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative

causes, there is insufficient evidence (information) to suggest a causal relationship.

The proportions of subjects who experienced TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching placebo) was █% in the upadacitinib arm and █% in the placebo arm through Week 52 (SS1) (Table 15).^{21,120} While the upadacitinib arm exhibited a numerically higher proportion of TEAEs, their interpretation requires caution, as their relatedness to corticosteroids was investigator-assessed, and all subjects had generally received high doses of corticosteroids prior to baseline. Generally, granular event recording by preferred term (PT) shows similar proportions of TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching placebo) between the upadacitinib and placebo arms, while small differences in individual PTs culminates in larger differences per system, organ, class (SOC) and overall.

The most common TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching placebo) by SOC were infections and infestations (upadacitinib: █%; placebo: █%), vascular disorders (upadacitinib: █%; placebo: █%), and eye disorders (upadacitinib: █%; placebo: █%).^{21,120} Most TEAEs by individual PT were low, with none reported in ≥ 10% subjects.^{21,120} Treatment emergent adverse events of oedema peripheral and cataracts were reported in the upadacitinib arm (█% and █%, respectively), with no cases in the placebo arm.^{21,120} The CTCAE grades for TEAEs of cataracts were all ≤ Grade 2 (mild to moderate), and there was only one Grade 3.^{21,120}

Table 15. Summary of TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching PBO) occurring in ≥ 5% of subjects in the SS1 by SOC and PT in any treatment group

Treatment-emergent events, n (%)	Total population	
	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 112	N = 209
Any AE	████	████

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Eye disorders		
Blepharitis		
Cataract		
Glaucoma		
Ocular hypertension		
Vision blurred		
Gastrointestinal disorders		
Abdominal pain upper		
Diarrhoea		
Dyspepsia		
Gastrooesophageal reflux disease		
Nausea		
General disorders and administration site conditions		
Chest pain		
Oedema peripheral		
Infections and infestations		
COVID-19		
Cystitis		
Folliculitis		
Herpes zoster		
Herpes zoster oticus		
Nasopharyngitis		
Ophthalmic herpes zoster		
Oral candidiasis		
Oral fungal infection		
Oral herpes		
Paronychia		
Rhinitis		
Sinusitis		
Tooth infection		
Upper respiratory tract infection		
Urinary tract infection		

Injury, poisoning and procedural complications		
Contusion		
Skin laceration		
Spinal compression fracture		
Investigations		
Blood cholesterol increased		
Weight increased		
Metabolism and nutrition disorders		
Diabetes mellitus		
Steroid diabetes		
Musculoskeletal and connective tissue disorders		
Arthralgia		
Back pain		
Muscle spasms		
Myopathy		
Osteopenia		
Osteoporosis		
Nervous system disorders		
Dizziness		
Headache		
Tremor		
Psychiatric disorders		
Anxiety		
Insomnia		
Substance-induced psychotic disorder		
Respiratory, thoracic and mediastinal disorders		
Cough		
Dyspnoea		
Epistaxis		
Pulmonary embolism		
Skin and subcutaneous tissue disorders		
Acne		

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Alopecia	████	████
Dry skin	█	████
Hirsutism	█	████
Hyperhidrosis	████	████
Perioral dermatitis	█	████
Rash	████	████
Vascular disorders	████	████
Deep vein thrombosis	████	████
Giant cell arteritis	████	████
Haematoma	████	████
Hypertension	████	████

Notes: TEAEs were defined as any AE with an onset or worsening in severity date after initiation of study drug and no more than 30 days after the last dose of study drug in the study. TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching placebo) were defined by consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

Table depicts the most related adverse event for each preferred term as assessed by the investigator for each subject.

Subjects were counted once in each row, regardless of the number of events they may have experienced.

Treatment emergent adverse event with an $n \leq 1$ are not tabulated for conciseness.

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

Abbreviations: CS-T, corticosteroid taper; PBO, placebo; PT, preferred term; SOC, system, organ, class; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report appendix, Table 909.4_01.01.01¹²⁰

2.11.2 Long-term safety analysis set (SS_LT)

The SELECT-GCA trial period 2 was completed in █████, with the available preliminary analysis of the safety data (SS_LT) up to the 06 February 2024 data cutoff shown in this section (████% of subjects having █████ weeks of exposure to upadacitinib).²¹

2.11.2.1 Summary of treatment emergent adverse events – SS_LT

Upadacitinib 15 mg was generally well-tolerated during the long-term extension (SS_LT) with a safety profile consistent to Period 1 (SS1). The proportions of subjects who experienced any TEAEs, SAEs, or TEAEs leading to discontinuation of study drug were generally similar between upadacitinib 15 mg arm (100%, 22.8%,

and 9.8%, respectively) and the placebo arm (95.3%, 25.6%, and 9.3%, respectively) (Table 16).²¹

Treatment emergent AEs were predominantly CTCAE ≤ Grade 2 (mild to moderate) in both treatment arms (65.1–69.5%).^{21,120} The proportion of subjects with TEAEs ≥ Grade 3 (severe to death) was similar between upadacitinib 15 mg and placebo arms (30.4% and 30.2%, respectively) (Table 16).^{21,120}

The proportion of subjects who experienced TEAEs with reasonable possibility of being related to upadacitinib (or matching placebo), as assessed by the investigator, was 56.5% in the upadacitinib 15 mg arm and 41.9% in the placebo arm (Table 16).^{21,120} The most common TEAEs considered by the investigator to have a reasonable possibility of being related to upadacitinib (or matching placebo) included increased blood creatine phosphokinase (upadacitinib: 8.7%; placebo: 0%), herpes zoster (upadacitinib: 4.3%; placebo: 4.7%) and urinary tract infections (upadacitinib: 5.4%; placebo: 4.7%).^{21,120}

The proportions of subjects who experienced TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching placebo), as assessed by the investigator, was 62.0% in the upadacitinib 15 mg arm and 58.1% in the placebo arm (Table 16);²¹ further details are provided in Appendix L.^{21,120}

There were no deaths reported in the long-term extension (SS_LT) (Table 16).^{21,120}

Table 16. Summary of TEAEs and deaths in the SS_LT

Treatment-emergent adverse events, n (%)	Total population	
	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 43	N = 92
Any adverse events (AE)	41 (95.3)	92 (100.0)
AE with reasonable possibility of being related to UPA (or matching PBO)	18 (41.9)	52 (56.5)

AE with reasonable possibility of being related to prednisone/prednisolone (or matching PBO)	25 (58.1)	57 (62.0)
AE by CTCAE Grade		
Grade 1	5 (11.6)	6 (6.5)
Grade 2	23 (53.5)	58 (63.0)
Grade 3	12 (27.9)	25 (27.2)
Grade 4	1 (2.3)	3 (3.3)
Grade 5	0	0
Serious AE	11 (25.6)	21 (22.8)
AE leading to withdrawal of UPA (or matching PBO)	4 (9.3)	9 (9.8)
COVID-19 related AE	11 (25.6)	24 (26.1)
AE results in death	0	0
All deaths	0	0
Occurring ≤ 30 days after last dose of study drug	0	0
COVID-19 related	0	0
Occurring > 30 days after last dose of study drug	0	0
COVID-19 related	0	0

Notes: TEAEs are defined as any AE with an onset or worsening in severity date after initiation of study drug and no more than 30 days after the last dose of study drug in the study.

Subjects are counted once in each row, regardless of the number of events they may have experienced.

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

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

Source: AbbVie data on file SELECT-GCA clinical study report appendix, Tables 908.4_01.01.01 and 910.4_02.01.02¹²⁰

The most common TEAEs (≥ 5% of subjects in any treatment arm) included COVID-19 (upadacitinib: 26.1%; placebo: 25.6%), arthralgia (upadacitinib: 25.0%; placebo: 30.2%), worsening of GCA (upadacitinib: 18.5%; placebo: 23.3%), back pain (upadacitinib: 17.4%; placebo: 18.6%), headache (upadacitinib: 20.7%; placebo: 14.0%), urinary tract infection (upadacitinib: 12.0%; placebo: 18.6%), hypertension (upadacitinib: 18.5%; placebo: 9.3%), nasopharyngitis (upadacitinib: 14.1%; placebo: 14.0%), pain in extremity (upadacitinib: 14.1%; placebo: 9.3%), upper respiratory

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tract infection (upadacitinib: 10.9%; placebo: 11.6%), osteoarthritis (upadacitinib: 12.0%; placebo: 9.3%), cough (upadacitinib: 8.7%; placebo: 11.6%), and dizziness (upadacitinib: 4.3%; placebo: 11.6%), (Table 17).²¹

Table 17. Summary of TEAEs occurring ≥ 5% of subjects (PT) in the SS_LT by SOC and PT in any treatment group

Treatment-emergent adverse events, n (%)	Total population	
	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 43	N = 92
Any AE	41 (95.3)	92 (100)
Blood and lymphatic system disorders	2 (4.7)	14 (15.2)
Anaemia	1 (2.3)	7 (7.6)
Ear and labyrinth disorders	3 (7.0)	11 (12.0)
Vertigo	1 (2.3)	7 (7.6)
Eye disorders	16 (37.2)	29 (31.5)
Cataract	3 (7.0)	8 (8.7)
Gastrointestinal disorders	17 (39.5)	43 (46.7)
Abdominal pain upper	3 (7.0)	9 (9.8)
Constipation	3 (7.0)	5 (5.4)
Diarrhoea	0	8 (8.7)
Dyspepsia	1 (2.3)	6 (6.5)
Gastroesophageal reflux disease	1 (2.3)	5 (5.4)
General disorders and administration site conditions	12 (27.9)	34 (37.0)
Chest pain	0	6 (6.5)
Fatigue	3 (7.0)	8 (8.7)
Oedema peripheral	2 (4.7)	6 (6.5)
Infections and infestations	32 (74.4)	69 (75.0)
COVID-19	11 (25.6)	24 (26.1)
Cystitis	2 (4.7)	9 (9.8)
Gastroenteritis	3 (7.0)	0

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Herpes zoster	2 (4.7)	5 (5.4)
Nasopharyngitis	6 (14.0)	13 (14.1)
Pneumonia	2 (4.7)	4 (4.3)
Sinusitis	2 (4.7)	5 (5.4)
Upper respiratory tract infection	5 (11.6)	10 (10.9)
Urinary tract infection	8 (18.6)	11 (12.0)
Injury, poisoning and procedural complications	12 (27.9)	29 (31.5)
Contusion	1 (2.3)	6 (6.5)
Fall	2 (4.7)	8 (8.7)
Investigations	12 (27.9)	25 (27.2)
Blood creatine phosphokinase increased	0	8 (8.7)
Metabolism and nutrition disorders	4 (9.3)	20 (21.7)
Hypercholesterolaemia	0	5 (5.4)
Musculoskeletal and connective tissue disorders	29 (67.4)	60 (65.2)
Arthralgia	13 (30.2)	23 (25.0)
Back pain	8 (18.6)	16 (17.4)
Intervertebral disc protrusion	3 (7.0)	1 (1.1)
Muscle spasms	4 (9.3)	6 (6.5)
Myalgia	2 (4.7)	6 (6.5)
Neck pain	4 (9.3)	4 (4.3)
Osteoarthritis	4 (9.3)	11 (12.0)
Osteoporosis	3 (7.0)	5 (5.4)
Pain in extremity	4 (9.3)	13 (14.1)
Neoplasms benign, malignant, and unspecified	4 (9.3)	14 (15.2)
Squamous cell carcinoma of skin	0	5 (5.4)
Nervous system disorders	16 (37.2)	38 (41.3)
Dizziness	5 (11.6)	4 (4.3)
Headache	6 (14.0)	19 (20.7)
Renal and urinary disorders	8 (18.6)	5 (5.4)

Haematuria	3 (7.0)	1 (1.1)
Respiratory, thoracic and mediastinal disorders	8 (18.6)	20 (21.7)
Cough	5 (11.6)	8 (8.7)
Skin and subcutaneous tissue disorders	14 (32.6)	31 (33.7)
Acne	0	6 (6.5)
Rash	2 (4.7)	8 (8.7)
Vascular disorders	17 (39.5)	31 (33.7)
Giant cell arteritis	10 (23.3)	17 (18.5)
Haematoma	3 (7.0)	1 (1.1)
Hypertension	4 (9.3)	17 (18.5)

Notes: TEAEs are defined as any AE with an onset or worsening in severity date after initiation of study drug and no more than 30 days after the last dose of study drug in the study.

Subjects are counted once in each row, regardless of the number of events they may have experienced.

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

Abbreviations: CS-T, corticosteroid taper; PBO, placebo; PT, preferred term; SOC, system, organ, class; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report, Table 14.3_1.8.4²¹

2.11.2.2 Treatment emergent adverse events leading to discontinuation of study drug – SS_LT

The proportion of subjects experiencing TEAEs leading to study drug discontinuation was 9.8% in the upadacitinib 15 mg and 9.3% in the placebo arm during the long-term extension (SS_LT) (Table 18).^{21,120}

Table 18. Summary of TEAE leading to discontinuation of study drug reported SS_LT by PT

Treatment-emergent adverse events, n (%)	Total population	
	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 43	N = 92
Any adverse event	4 (9.3)	9 (9.8)
Atrial fibrillation	0	1 (1.1)
Aortitis	1 (2.3)	0
Aspergillus infection	1 (2.3)	0

Company evidence submission template for upadacitinib for giant cell arteritis [ID6299]

Pneumonia	0	1 (1.1)
Diarrhoea	0	1 (1.1)
Diffuse alopecia	0	1 (1.1)
Fatigue	0	1 (1.1)
Foot fracture	0	1 (1.1)
Giant cell arteritis	1 (2.3)	1 (1.1)
Haemoglobin decreased	1 (2.3)	0
Osteoarthritis	0	1 (1.1)
Prostate cancer	0	1 (1.1)

Notes: TEAEs were defined as any AE with an onset or worsening in severity date after initiation of study drug and no more than 30 days after the last dose of study drug in the study.

Subjects are counted once in each row, regardless of the number of events they may have experienced.

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

Abbreviations: CS-T, corticosteroid taper; PBO, placebo; PT, preferred term; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report appendix¹²⁰

2.11.2.3 Adverse events of special interest – SS_LT

The AESIs identified based on upadacitinib findings across all indications and safety concerns reported for other JAK inhibitors were in general low and comparable between the SS1 and SS_LT. No treatment-emergent AESIs of active TB, lymphoma, neutropenia, adjudicated gastrointestinal perforation, or adjudicated MACE were reported in either treatment arm (Table 19).^{21,120}

The proportion of subjects who experienced AESI of serious infections was lower in the upadacitinib 15 mg arm (5.4%) compared with the placebo arm (11.6%).^{21,120}

Adverse event of special interest of opportunistic infection occurred in 1.1% and 2.3% of subjects in the upadacitinib 15 mg and placebo arms, respectively.^{21,120}

These events included *Aspergillus* infection (1 event in the placebo arm) and oesophageal candidiasis (1 event in the upadacitinib 15 mg arm).^{21,120} The *Aspergillus* infection was serious, severe and led to discontinuation of study drug.

The oesophageal candidiasis was nonserious, moderate, and did not result in discontinuation of study drug.^{21,120}

The proportion of subjects who experienced AESI of herpes zoster was higher in the upadacitinib 15 mg arm (6.5%) compared with placebo arm (4.7%).^{21,120} Similar to Period 1 (SS1), most subjects had one dermatome involvement, and no event had CNS involvement.

The proportion of subjects who experienced AESI of malignancy was 6.5% in the upadacitinib 15 mg arm and 4.7% in the placebo arm.^{21,120} Nonmelanoma skin cancer (NMSC) events included squamous cell carcinoma of skin (5 events in the upadacitinib 15 mg arm) and basal cell carcinoma (2 events in the placebo arm and 1 event in the upadacitinib 15 mg arm).^{21,120} No events of NMSC led to discontinuation of the study drug. Malignancies excluding NMSC events included lentigo maligna (1 event in the upadacitinib 15 mg arm [same event described above under Period 1 SS1]), prostate cancer (1 in the upadacitinib 15 mg arm).^{21,120} All events of malignancy resulted in discontinuation of the study drug except for lentigo maligna.

The proportion of subjects who experienced AESI of anaemia was 12.0% in the upadacitinib 15 mg arm and 7.0% in the placebo arm, respectively.^{21,120} A single AESI of lymphopenia was reported in the upadacitinib 15 mg arm.^{21,120} These events were non-serious, severe, and resolved without discontinuation of study drug.

Adverse event of special interest of creatine kinase elevations were only reported in the upadacitinib 15 mg arm (8.7%).^{21,120} No event of rhabdomyolysis was reported.

One non-fatal event of adjudicated VTE (pulmonary embolism) was reported in the upadacitinib 15 mg arm in a subject with multiple risk factors for VTE.^{21,120} The event was serious, severe, but did not result in discontinuation of the study drug.

Table 19. Summary of treatment-emergent AESI in the SS_LT by PT

Treatment-emergent adverse events, n (%)	Total population

Company evidence submission template for upadacitinib for giant cell arteritis [ID6299]

	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 43	N = 92
Serious infections	5 (11.6)	5 (5.4)
Opportunistic infection excluding TB and herpes zoster	1 (2.3)	1 (1.1)
Herpes zoster	2 (4.7)	6 (6.5)
Malignancy	2 (4.7)	6 (6.5)
NMSC	2 (4.7)	5 (5.4)
Malignancy excluding NMSC	0	2 (2.2)
Anaemia	3 (7.0)	11 (12.0)
Lymphopenia	0	1 (1.1)
Renal dysfunction	1 (2.3)	0
Hepatic disorder	3 (7.0)	5 (5.4)
CPK elevation	0	8 (8.7)
Adjudicated embolic and thrombotic events (non-cardiac, non-CNS)	0	1 (1.1)
VTE [‡]	0	1 (1.1)

Notes: TEAEs were defined as any AEs with an onset or worsening in severity date after initiation of study drug and no more than 30 days after the last dose of study drug in the study.

Subjects are counted once in each row, regardless of the number of events they may have experienced.

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

[†] MACE was defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

[‡] VTE included deep vein thrombosis and pulmonary embolism (fatal and non-fatal).

Abbreviations: CS-T, corticosteroid taper; PBO, placebo; PT, preferred term; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report appendix, Table 908.4_02.01.01¹²⁰

2.11.2.4 Corticosteroid-related adverse events – SS_LT

The proportions of subjects who experienced TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching placebo), as assessed by the investigator, was 62.0% in the upadacitinib 15 mg arm and 58.1% in the placebo arm during the long-term extension (SS_LT) (Table 20).^{21,120} While the upadacitinib 15 mg arm exhibited a numerically higher proportion of TEAEs, as described in Section 2.11.1.4, their interpretation requires caution, as their relatedness to corticosteroids Company evidence submission template for upadacitinib for giant cell arteritis [ID6299]

was investigator-assessed, and all subjects had generally received high doses of corticosteroids prior to baseline.

The most common TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching placebo) by SOC were infections and infestations (upadacitinib: 30.4%; placebo: 27.9%), vascular disorders (upadacitinib: 13.0%; placebo: 14.0%), and skin and subcutaneous tissue disorders (upadacitinib: 12.0%; placebo: 7.0%) (Table 20).^{21,120} As observed in Period 1 (SS1) most TEAEs by individual PT were low, with none reported in $\geq 10\%$ subjects. Treatment emergent AEs of oedema peripheral were reported in the upadacitinib 15 mg arm (4.3%), with no cases in the placebo arm, although, TEAEs of cataracts were equivalent between upadacitinib 15 mg (2.2%) and placebo (2.3%) (Table 20).^{21,120} The CTCAE grades for TEAEs of oedema peripheral and cataracts were all $\leq$ Grade 2 (mild to moderate).^{21,120}

Table 20. Summary of TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching PBO) occurring in $\geq 5\%$ subjects in the SS_LT by SOC and PT in any treatment group

Treatment-emergent events, n (%)	Total population	
	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 43	N = 92
Any adverse event	25 (58.1)	57 (62.0)
Cardiac disorders	0	5 (5.4)
Cardiac failure	0	3 (3.3)
Eye disorders	3 (7.0)	10 (10.9)
Blepharitis	0	2 (2.2)
Cataract	1 (2.3)	2 (2.2)
Gastrointestinal disorders	4 (9.3)	9 (9.8)
Abdominal pain upper	2 (4.7)	3 (3.3)
Dyspepsia	0	2 (2.2)
General disorders and administration site conditions	1 (2.3)	6 (6.5)
Oedema peripheral	0	4 (4.3)

Infections and infestations	12 (27.9)	28 (30.4)
Cystitis	1 (2.3)	3 (3.3)
Herpes zoster	1 (2.3)	3 (3.3)
Nasopharyngitis	1 (2.3)	3 (3.3)
Oral candidiasis	0	2 (2.2)
Oral herpes	0	3 (3.3)
Paronychia	2 (4.7)	2 (2.2)
Upper respiratory tract infection	0	4 (4.3)
Urinary tract infection	2 (4.7)	4 (4.3)
Injury, poisoning and procedural complications	2 (4.7)	5 (5.4)
Contusion	0	3 (3.3)
Investigations	4 (9.3)	6 (6.5)
Weight increased	2 (4.7)	3 (3.3)
Metabolism and nutrition disorders	2 (4.7)	6 (6.5)
Steroid diabetes	1 (2.3)	2 (2.2)
Musculoskeletal and connective tissue disorders	3 (7.0)	9 (9.8)
Osteopenia	0	2 (2.2)
Osteoporosis	2 (4.7)	4 (4.3)
Psychiatric disorders	3 (7.0)	3 (3.3)
Respiratory, thoracic and mediastinal disorders	1 (2.3)	6 (6.5)
Cough	0	2 (2.2)
Skin and subcutaneous tissue disorders	3 (7.0)	11 (12.0)
Acne	0	5 (5.4)
Rash	0	2 (2.2)
Vascular disorders	6 (14.0)	12 (13.0)
Giant cell arteritis	2 (4.7)	7 (7.6)
Haematoma	2 (4.7)	0
Hypertension	4 (9.3)	7 (7.6)

Notes: TEAEs were defined as any AE with an onset or worsening in severity date after initiation of study drug and no more than 30 days after the last dose of study drug in the study. TEAEs with reasonable possibility of being related to prednisone/prednisolone (or matching placebo) were defined by consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

Table depicts the most related adverse event for each preferred term as assessed by the investigator for each subject.

Subjects were counted once in each row, regardless of the number of events they may have experienced.

Company evidence submission template for upadacitinib for giant cell arteritis [ID6299]

Treatment emergent adverse event with an n ≤ 1 are not tabulated for conciseness.

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

Abbreviations: CS-T, corticosteroid taper; PBO, placebo; PT, preferred term; SOC, system, organ, class; UPA, upadacitinib, WK, week

Source: AbbVie data on file SELECT-GCA clinical study report appendix, Table 909.4_01.01.02¹²⁰

2.11.2.5 Extent of exposure – SS_LT

Up to the 06 February 2024 data cutoff, in the SS_LT, which includes subjects who received the same treatment in period 1 and period 2, the mean duration of upadacitinib 15 mg exposure was [REDACTED] days, with [REDACTED]% of subjects having ≥ [REDACTED] weeks of exposure to upadacitinib 15 mg (Table 21).²¹

Table 21. Extent of exposure in the SS_LT

Duration (days)	Total population	
	PBO + 52 WK CS-T	UPA + 26 WK CS-T
	N = 43	N = 92
Mean (SD)	[REDACTED]	[REDACTED]
Median	[REDACTED]	[REDACTED]
Min, Max	[REDACTED]	[REDACTED]
Duration (weeks) - n (%)		
≥ 1 day	[REDACTED]	[REDACTED]
≥ 2 weeks	[REDACTED]	[REDACTED]
≥ 4 weeks	[REDACTED]	[REDACTED]
≥ 12 weeks	[REDACTED]	[REDACTED]
≥ 24 weeks	[REDACTED]	[REDACTED]
≥ 36 weeks	[REDACTED]	[REDACTED]
≥ 48 weeks	[REDACTED]	[REDACTED]
≥ 52 weeks	[REDACTED]	[REDACTED]
≥ 60 weeks	[REDACTED]	[REDACTED]
≥ 72 weeks	[REDACTED]	[REDACTED]
≥ 84 weeks	[REDACTED]	[REDACTED]

Company evidence submission template for upadacitinib for giant cell arteritis [ID6299]

≥ 96 weeks		

Note: Duration of treatment = last dose date - first dose date + 1

PBO + 52 WK CS-T = placebo + 52 weeks corticosteroid taper; UPA + 26 WK CS-T = upadacitinib 15 mg + 26 weeks corticosteroid taper

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

Source: AbbVie data on file SELECT-GCA clinical study report, Table 14.1_9.2²¹

2.12 Ongoing studies

The SELECT-GCA trial concluded in [REDACTED] and this submission presents the most recent data cutoff for 06 February 2024 and includes all subjects who completed Period 1 and approximately 61% of subjects who have completed Period 2.

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal findings from the clinical evidence

Patients with GCA are at risk of vision loss, vascular complications, and increased all-cause mortality.^{1,51} Early diagnosis and rapid initial treatment are crucial to improve the overall prognosis, and the treatment aims of GCA are to reduce relapses and induce sustained remission. However, treatment options are limited, with long-term corticosteroids the main treatment for most patients. Ultimately, patients experience recurrent disease relapses,^{2,3,36} high cumulative corticosteroid doses, and the associated burden of corticosteroid-related AEs.^{26,127} In line with clinical expert opinion, upadacitinib is anticipated to provide an alternative long-term treatment option to corticosteroids for GCA patients.

Results from the SELECT-GCA trial demonstrate that upadacitinib 15 mg with a 26-week corticosteroid taper is superior to placebo and a 52-week corticosteroid taper in Period 1.^{21,23} A significantly greater proportion of subjects achieved the primary endpoint of sustained remission at Week 52 with upadacitinib 15 mg.^{21,23}

Upadacitinib 15 mg was also associated with significant improvements in the key secondary endpoints, including a greater proportion of subjects who achieved

Company evidence submission template for upadacitinib for giant cell arteritis [ID6299]

sustained complete remission at Week 52.^{21,23} Upadacitinib 15 mg reduced the proportion of subjects who experienced at least one GCA flare, the number of flares per subject, and the time to first flare at Week 52.^{21,23} Upadacitinib 15 mg also demonstrated a corticosteroid-sparing effect, with reductions in the overall median cumulative corticosteroid exposure and in the additional corticosteroid treatment needed to treat disease relapse above the predefined taper over the course of the trial.^{21,23}

Treatment with upadacitinib 15 mg resulted in a significant improvement in HRQoL outcomes for patients with GCA.^{21,23} There was a significant improvement in physical health status as measured by SF-36 PCS, and fatigue using the FACIT fatigue scale at Week 52.^{21,23} A numerical improvement in health status from baseline was also demonstrated by the EQ-5D Index and VAS scores.²¹ Although, the results for EQ-5D Index and VAS scores reached nominal statistical significance, it cannot be formally claimed as such because higher-ranked endpoints in the hierarchical testing were not significant.

The safety analysis of SELECT-GCA demonstrated that upadacitinib 15 mg was generally well-tolerated, through Week 52 in Period 1 (SS1) and the long-term safety analysis set (SS_LT) (65.2% of subjects having ≥ 96 weeks of exposure to upadacitinib).^{21,23} The safety profile was consistent with the known safety profile derived from randomised clinical trials with over 15,000 patient-years of treatment exposure in multiple indications.^{21,23,118,119} Treatment emergent adverse events were low and generally balanced across treatment arms in both SS1 and SS_LT.^{21,23} The majority of TEAEs were grade ≤ 2 in severity.²¹ In the SS1 and SS_LT, the proportion of TEAEs leading to study drug discontinuation was low across both arms.²¹ Among AESI, identified based on upadacitinib findings across all indications and safety concerns reported for other JAK inhibitors, no cases of adjudicated MACE were reported in the upadacitinib 15 mg arm, compared to two occurring in the placebo arm for the SS1.^{21,23} In the SS_LT, no cases of adjudicated MACE were reported in

either arm.²¹ The proportion of subjects that experienced a non-fatal VTE was comparable between arms, at 3.3% in the upadacitinib 15 mg arm and 3.6% in the placebo arm in SS1,^{21,23} and in the SS_LT period only one non-fatal VTE occurred in the upadacitinib 15 mg arm, in a patient with multiple risk factors for VTE.²¹ The rates of serious infections were lower in the upadacitinib 15 mg than placebo arm in both the SS1 and SS_LT.^{21,23} Treatment emergent deaths were low in SS1, with 2 each in the upadacitinib 15 mg arm and placebo arm.^{21,23} In the upadacitinib 15 mg arm one death was attributed to COVID-19 and the other was adjudicated as an unexplained cause.^{21,23} No treatment emergent deaths occurred in the SS_LT.²¹

GCA places a considerable burden upon patients due to the risk of vision loss, increased all-cause mortality, cumulative long-term corticosteroid exposure and associated AEs, and limited treatment options, all of which severely impact their quality of life.^{36,54,68} In the SELECT-GCA trial upadacitinib demonstrated efficacy in inducing sustained disease remission, preventing flares, reducing cumulative corticosteroid exposure, and improving HRQoL in all patients with GCA.^{21,23} Furthermore, upadacitinib was generally well-tolerated with a safety profile consistent with the known safety profile derived from previous randomised clinical trials in multiple indications.^{21,23,118,119} These results demonstrate the potential of upadacitinib as a long-term corticosteroid-sparing therapy for all patients with GCA.

2.13.2 Strengths and limitation of the clinical evidence base

2.13.2.1 Strengths

The SELECT-GCA trial was a robust study with a double-blind placebo-controlled phase (Period 1) and a 52-week blinded extension (Period 2). The trial was designed with appropriate sample sizes, power, statistical analysis, multiple endpoints, and length of follow-up (up to 104 weeks on treatment for participants in the blinded extension), which allows for the rigorous evaluation of efficacy and safety data.²¹⁻

23,126

The SELECT-GCA trial populations were predominantly European (including participants in the UK) and north American which make the results generalisable to a UK population.^{21,23} The overall mean age in the trial, 71 years,^{21,23} is close to the 73 years estimated by the CPRD for the UK.²⁷ Clinical expert opinion from clinicians in the UK agreed that the trial demographics were reflective on a UK population.

The SELECT-GCA trial reported a range of efficacy endpoints to assess the clinical benefit to patients with GCA, and includes those specified in the NICE decision problem (Section 1.1).^{21,23} The primary endpoint was sustained remission, a measure of disease activity (GCA sign and symptoms) and ability to adhere to corticosteroid taper regimen,^{21,23} which is a clinically meaningful and commonly utilised endpoint in clinical trials for treatments in patients with GCA.¹²⁸ The multiplicity-controlled secondary endpoints included disease flare or relapse-related endpoints, including the proportion of subjects who experienced at least one GCA flare, number of flares per subject, cumulative corticosteroid dose, and time to first GCA flare.^{21,23} These were clinically relevant and investigator determined based on recurrence of GCA signs or symptoms or an ESR measurement > 30 mm/hr (attributable to GCA) and required an increase in corticosteroid dose.^{21,23}

The SELECT-GCA trial provides extensive safety data through Week 52 in Period 1 (SS1) and the long-term safety analysis set (SS_LT) (65.2% of subjects having ≥ 96 weeks of exposure to upadacitinib).^{21,23}

2.13.2.2 Limitations

The SELECT-GCA trial used corticosteroid tapering regimens of 52-weeks.^{21,23} While this is in the lower bound of the BSR guidelines,² which recommend tapering over 12–18 months, UK clinical expert opinion has suggested wide variability exists in clinical practice, with tapering regimens largely down to clinician preference guided by individual patient characteristics and GCA disease course.

The SELECT-GCA trial had a higher-than-expected proportion of subjects who discontinued upadacitinib 15 mg (26%) or placebo (37%) in Period 1.^{21,23} These high percentages could be attributed to the timing of the trial during the Covid-19 pandemic, when older patients were less inclined to leave their homes to visit trial sites, and to the approval of tocilizumab for GCA, which may have led some patients to opt for an already approved therapy.

Although patients with prior corticosteroid toxicity and patients who have had up to 12 months of tocilizumab and who are unsuitable for tocilizumab are not considered separately explicitly, clinical expert opinion emphasised these patients will still receive corticosteroids in clinical practice to control disease flare given the lack of alternative treatment options and risk of serious GCA related complications without treatment. Nevertheless, these patients are captured within the GCA population addressed in the company submission.

While the upadacitinib 15mg arm exhibited a numerically higher proportion of TEAEs in SELECT-GCA, their interpretation requires caution, as their relatedness to corticosteroids was investigator-assessed, and all subjects had generally received high doses of corticosteroids before baseline.^{21,23} Moreover, the short duration of the trial (Period 1 – 52-weeks) and the potential for increased cardiovascular risk in patients with GCA highlights the need for long-term safety assessments. The 52-week blinded extension (Period 2) period of the trial will provide additional data on the safety of upadacitinib through 2 years.

3 Cost effectiveness

A cost-utility analysis was performed using a semi-Markov model structure in line with the previous NICE appraisal in GCA (TA518)

- The objective of this analysis was to evaluate the cost-effectiveness of upadacitinib in patients with GCA. The analysis compares upadacitinib (15 mg) + 26-week corticosteroid tapering with 52-week corticosteroid tapering alone. Corticosteroids are the main treatment available to all GCA patients and are considered the relevant comparator in this appraisal.
- As highlighted by NICE scope consultees,⁴⁷ recent publications from TOC STOP,²⁸ and clinical expert feedback, there is a major unmet need for a corticosteroid-sparing therapy with flexible treatment duration for GCA patients. In the base case analysis, a treatment duration of 2 years was used for upadacitinib. However, the cost-effectiveness of upadacitinib was also demonstrated over a range of treatment durations, allowing the treatment duration to be tailored based on patient preference and clinician judgement according to disease activity.
- Given the impact of corticosteroid exposure and related AEs, the CEA included an updated list, relative to TA518, of corticosteroid-related AEs to appropriately capture the cumulative steroid burden on patients. As highlighted by clinical experts, the AE rates in SELECT-GCA trial do not fully represent the burden of corticosteroids due to the long-term nature of these AEs. As such, data from a longer-term RWE study were incorporated.
- A semi-Markov model was developed incorporating four health states:
 - Pre-flare remission
 - Flare
 - Post-flare remission
 - Death

Time to flare

- The transition from the pre-flare remission to the flare state was informed by the time to first flare (TTFF) outcome from the SELECT-GCA trial. Simple parametric models were used to extrapolate TTFF over the lifetime duration given the observed data from SELECT-GCA are available for a 52-week period.

- Patients who are in remission remain at a constant risk of experiencing subsequent flares, with a higher risk following the first flare. The probabilities of subsequent flares were estimated from SELECT-GCA.
- Patients remain in the flare state for 4-weeks, during which they return to their last effective dose of corticosteroids prior to flare before resuming tapering in the post-flare remission state. In line with clinician experience, it is assumed that a proportion of patients that flare will experience a 'severe' flare, and due to the severity restart corticosteroids at a higher dose than the last effective corticosteroid dose (20% restarting at 40 mg in the base case).
- All key model assumptions, including TTFF extrapolations, subsequent flare rates and tapering assumptions were validated with clinical experts and against the published literature where possible.

Disease burden

- To reflect the significant burden imposed upon patients with GCA, the model captures both GCA-related complications and corticosteroid-related AEs with their associated healthcare costs and disutilities.
- GCA-related complications—such as vision loss, stroke, or cardiovascular events—occur exclusively during the flare health state with event rates derived from the published literature.
- Increases in cumulative corticosteroid exposure are linked to increased risks in corticosteroid-related AEs in the model. Due to these AEs emerging over longer durations of corticosteroid exposure than those experienced in a trial setting, corticosteroid-related AE rates are derived from an RWE study. Clinical experts considered the study population, AEs included, and event rates reflective of GCA patients in the UK.
- Whilst not observed in SELECT-GCA, JAKi specific AEs are also incorporated into the analysis for patients treated with upadacitinib.

Utilities

- Health state utilities are derived from SELECT-GCA in the base case analysis, with a utility decrement between flare and remission of -0.0587 in the overall GCA population.
- A scenario analysis was conducted to explore the impact of informing health state utilities with data from GiACTA.

Cost-effectiveness results

- All cost-effectiveness results presented within this submission use the upadacitinib PAS price.
- In the base case analysis, upadacitinib was dominant and associated with an incremental gain of [REDACTED] QALYs and a cost saving of [REDACTED] per patient compared with a 52-week corticosteroid tapering regimen.
- Sensitivity analyses reinforced the robustness of the economic case for upadacitinib. Cost-effectiveness was preserved across variations in flare assumptions, treatment duration, utility values, and variation of selected corticosteroid-related AEs.
- Upadacitinib remained dominant or cost-effective even when treatment was modelled over extended durations (e.g. lifetime) and resulted in a lower cumulative corticosteroid exposure for patients over time.

Conclusions

- The results of the economic analysis presented in this submission demonstrate that upadacitinib represents an efficacious and cost-effective use of NHS resources compared to corticosteroid treatment in GCA patients.
- Upadacitinib treatment effectively reduces the rate of flares and the burden of cumulative corticosteroid use, thereby enhancing the quality of life for patients and decreasing resource utilisation
- Whilst the CEA aimed to capture the impacts of cumulative steroid burden and associated AEs, the full long-term effects and mortality risk associated with each event may be underestimated in the model.

3.1 Published cost-effectiveness studies

In line with the NICE technology evaluations manual, an SLR was conducted to identify all relevant cost-effectiveness studies in GCA. The SLR was conducted in alignment with the CRD's guidance for systematic reviews, the Cochrane Handbook for Systematic Reviews, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and requirements set out by NICE.¹²¹⁻¹²⁴ Details of the SLR are provided in Appendix E.

In brief, electronic databases (including Embase, Medline, PubMed and EconLit) were searched to retrieve studies from 2010 to 13 May 2024, and subsequently updated on 19 February 2025. Electronic database searches included abstracts

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indexed by the Northern Light database; conference proceedings between 2019 and April 2024 were also searched to identify cost-effectiveness studies relating to patients with GCA, including from the International Vasculitis Workshop and BSR annual conference. In addition, searches were performed on the websites of HTA authorities to retrieve critical appraisals and key learnings from previous assessments. HTA authorities considered included NICE, Canadian Agency for Drugs and Technologies in Health (CADTH), Scottish Medicines Consortium (SMC), Gemeinsamer Bundesausschuss/Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (G-BA/IQWiG), Haute Autorité de Santé (HAS), Pharmaceutical Benefits Advisory Committee (PBAC), National Institute for Health Research (NIHR) HTA library, and the International Network of Agencies for Health Technology Assessment (INAHTA) database. To identify relevant conference proceedings and articles, search terms for GCA were used in the website's search engines.

Literature searches were designed applying a combined approach to identify evidence relating to economic evaluations, costs and healthcare resource utilisation, and health state utility studies relating to adults with GCA. A PRISMA diagram for the original combined literature review (date-span 2010 to 10 May 2024) is presented in Figure 10. PRISMA diagram for the updated searches is presented in Appendix E; however, no additional evidence relating to economic evaluations were eligible for inclusion.

Of the included studies, ten presented economic evaluations in GCA. The evaluations predominantly utilised semi-Markov models to facilitate cost-utility analyses (CUA) of tocilizumab versus corticosteroids (n=8), including a NICE and SMC evaluation conducted from the perspective of NHS England/Scotland. Two studies reported evaluations of GCA diagnosis/screening practices, including a retrospective evaluation of fast-track versus conventional referral routes for GCA diagnosis in the UK. Most of the economic evaluations adopted a payer perspective, offering limited qualitative insight into societal consequences whilst being frequently noted for their impact in the GCA population by authors, indicating a research gap

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regarding broader healthcare impacts such as caregiver burden and associated costs for patients with GCA. A summary of published cost-effectiveness studies identified within the economic SLR is presented in Appendix E.

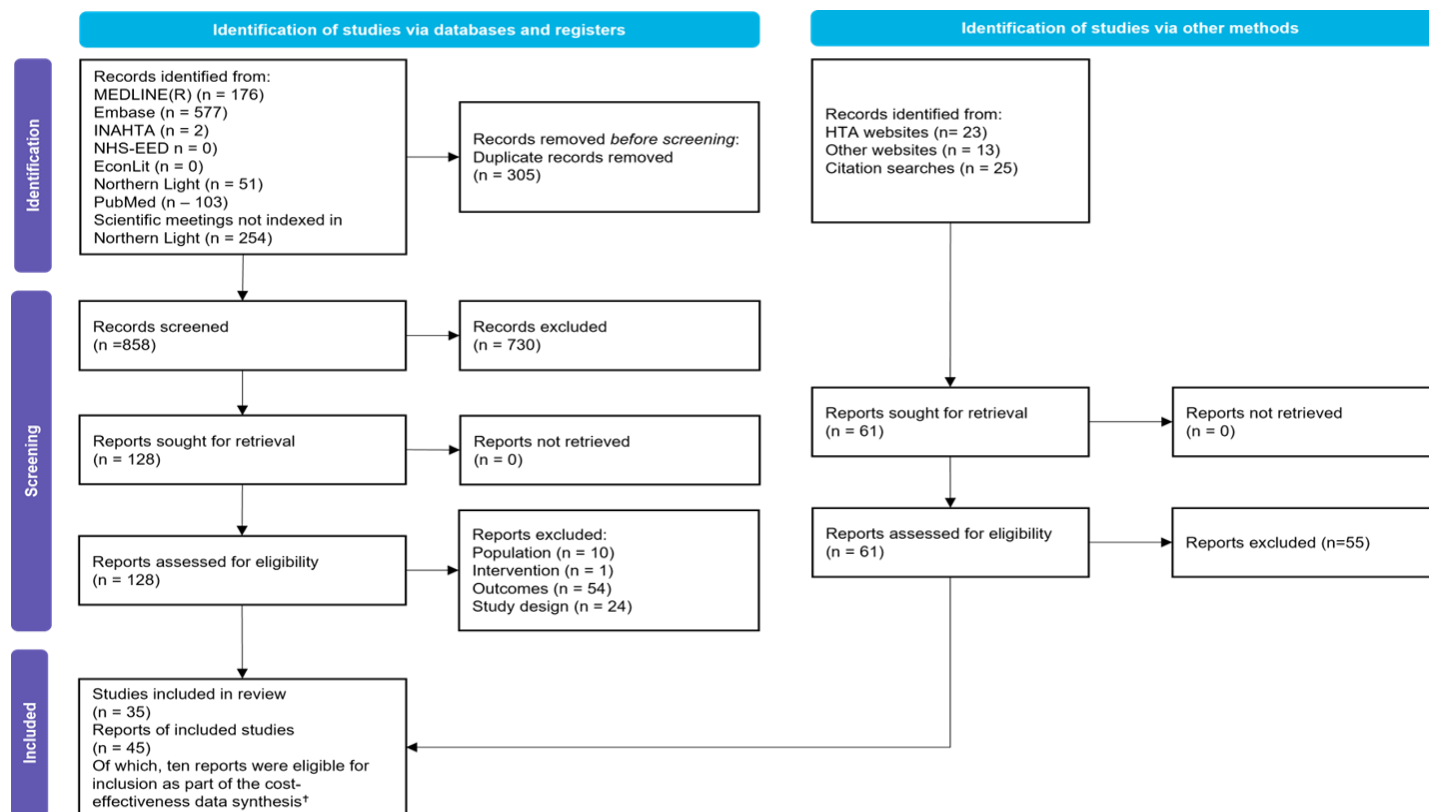


Figure 10. PRISMA diagram illustrating the study selection process for identifying cost-effectiveness studies for the original SLR (2010 to 10 May 2024)

† The remaining 35 reports were eligible for inclusion as part of the cost and healthcare resource utilisation review component and the health-related quality of life component, described in Appendix G and Appendix F, respectively.

3.2 Economic analysis

The economic case presented in this submission is based on a de novo cost-effective analysis (CEA), assessing the use of upadacitinib for the treatment of adults with GCA. The analysis considers the simple patient access scheme (PAS) discount available for upadacitinib.

3.2.1 Patient population

The population modelled reflects the intention-to-treat (ITT) analysis from SELECT-GCA, comprising adult patients with a diagnosis of active GCA. The proposed licensed dose of 15 mg daily of upadacitinib and the corresponding 26-week tapering schedule were incorporated, alongside the placebo arm with 52-week corticosteroid tapering.

As per the NICE scope, the cost-effectiveness in the new onset and relapsing GCA subgroups were explored and are included in Appendix C. While the final NICE scope outlines subgroups such as “tocilizumab unsuitable” and “steroid unsuitable,” these populations are not modelled explicitly. Given the standard of care for these patients is also corticosteroids, these subgroups are captured indirectly within the modelled GCA patient population. Therefore, the model framework is structured to capture all patients with an unmet need for treatment.

In summary, the ITT population modelled in the base case captures all GCA patients set to benefit from treatment with upadacitinib and ensures alignment with contemporary clinical practice and the decision problem outlined in the final NICE scope.

3.2.1.1 Baseline characteristics

Based on the patient population in SELECT-GCA, patients entering the model were 71.1 years old, with a mean weight of 69.3 kg and with female patients comprising 73.1% of the population.²¹ Table 22 shows the distribution of the initial corticosteroid

dose at baseline, defined as 8 weeks after new-onset diagnosis or relapse in SELECT-GCA.^{21,22}

Table 22. Initial dose of corticosteroid by treatment arms

Proportion of patients with different initial dose of CS	UPA + 26 WK CS-T	PBO + 52 WK CS-T
60 mg	9.57%	5.36%
50 mg	9.09%	14.29%
40 mg	28.71%	27.68%
30 mg	22.97%	25.89%
20 mg	29.67%	26.79%

Abbreviations: CS-T, corticosteroid tapering; PBO, placebo; UPA, upadacitinib, WK, week
Source: AbbVie data on file SELECT-GCA clinical study report,²¹ and Collinson et al.¹²⁹

3.2.2 Model structure

As noted in Section 3.1, several published CEAs were identified evaluating the cost-effectiveness of tocilizumab versus corticosteroids using a semi-Markov model framework across different country settings. The CEA informing NICE TA518 was reported in detail and considered the most relevant published model to the UK setting and the SoC treated population being considered in the present appraisal. Building upon the CEA informing TA518, a de-novo model (Figure 11) was developed for this appraisal. The model was developed based on the known pathophysiology of GCA, SELECT-GCA data,²¹ and capturing NICE committee and EAG preferences from TA518. Clinician input was sought throughout to validate and inform any assumptions required to better reflect contemporary clinical practice for GCA.

The model was developed in Microsoft Excel 365® as a semi-Markov cohort model with a weekly cycle length. No half-cycle correction was applied as the weekly cycle length was considered sufficiently granular to capture changes in disease status and flare occurrence/resolution. The model is comprised of four mutually exclusive health states, with death as the absorbing state:

- Pre-flare remission

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- Flare
- Post-flare remission
- Death

Patients with GCA enter the model in the pre-flare remission state and initiate treatment with upadacitinib (15 mg daily) + 26-week corticosteroid tapering, or 52-week corticosteroid tapering alone. Patients remain in the pre-flare remission state until their first flare, as defined in the SELECT-GCA trial. The transition from the pre-flare remission state to the flare state is informed by the secondary endpoint from SELECT-GCA, time to first flare (TTFF).²¹

Following first flare, patients transition to the post-flare remission health state. During remission, they follow the corticosteroid tapering schedules pre-defined in SELECT-GCA.^{21,91} To counter the 'memoryless' nature of a Markov model, the post-flare remission state incorporated 52 tunnel states to track the corticosteroid dose applied in each weekly cycle to match the 52-week corticosteroid tapering schedule.

Patients who are in remission remain at risk of experiencing subsequent flares, with a higher risk following the first flare. The probabilities of subsequent flares for patients treated with upadacitinib + 26-week corticosteroid tapering and placebo + 52-week corticosteroid tapering were estimated based on the SELECT-GCA trial.²¹ The duration of flare was assumed to be 4 weeks, following the committee preferred duration reported in TA518 and validated through consultation with clinical experts.

In the aftermath of a flare, clinical expert advice was followed regarding the immediate likelihood of a subsequent flare and the accompanying corticosteroid dose. It is assumed that during the 4 weeks following flare, patients are not subject to the probability of a further flare and instead revert to their last effective corticosteroid dose, defined as that received in the week preceding the flare for the 4-week flare period. This 'during flare' period is defined by a series of 4 tunnel states to delineate each week following the flare. Patients are assumed to continue their last effective

dose for an additional week in the post-flare remission state (unless death occurs) before resuming the corticosteroid-tapering schedule.

Feedback from clinical experts indicated that of the patients that experience flares, a proportion of these are severe and require escalation to a higher corticosteroid dose (closer to their initial starting dose), rather than simply reverting to their previous pre-flare 'last effective dose'. Clinical experts consulted at the advisory board noted that of patients experiencing flare, approximately 20% of these will be severe. These observations are supported by the TOCSTOP study, where in a cohort of relapsing and refractory GCA patients, 33.6% of relapses were severe (as defined by EULAR criteria).²⁸ By differentiating between 'minor' and 'severe' flares, the model captures the additional corticosteroid exposure and associated AEs (such as increased cardiovascular risks and metabolic complications) for patients who experience severe flares.

Additionally, the model captures both GCA-related complications and corticosteroid-related AEs, recognising their distinct clinical implications. GCA-related complications—such as vision loss, stroke, or cardiovascular events—are assumed to occur exclusively during the flare health state, while corticosteroid-related AEs can occur in any health state except death, reflecting the systemic and cumulative burden of long-term steroid use. To more accurately reflect this burden, the model incorporates corticosteroid-related AEs based on cumulative corticosteroid exposure. Although the SELECT-GCA trial reported very few acute or long-term corticosteroid-related AEs due to the long-term nature of these events, RWE suggests that these events emerge over longer durations of exposure. Therefore, data were sourced from a large-scale US-based retrospective study using the IBM Watson Health MarketScan Commercial and Medicare databases, which analysed AE incidence across different corticosteroid dose bands over a follow-up period of up to 5 years.⁴⁴ This approach aligns with clinical feedback and the methodology for deriving corticosteroid related AEs accepted in TA518, similarly necessitated due to limited follow up from their clinical trial. Further details on the real-world evidence study and AE incidence rate derivation are reported in section 3.3.2.2.

The cumulative corticosteroid dose in the model is estimated in three steps: (1) calculating the average corticosteroid dose for each health state; (2) multiplying that average dose by the proportion of patients in each health state per cycle; and (3) summing the cumulative dose from previous and current cycles. Based on this evolving cumulative dose, the model applies AE incidence rates specific to steroid dosage bands, in line with both real-world data and thresholds validated by UK clinicians.

For patients experiencing AEs—whether GCA- or corticosteroid-related—the model applies both direct healthcare costs and disutilities, ensuring that the clinical and economic burden is fully captured. While the model includes a comprehensive list of relevant AEs, it is acknowledged that the estimates are conservative, and some steroid-related events may not be fully captured due to limitations in the source data.

Death is an absorbing state in the model, with patients transitioning to death from any health state. Treatments for GCA are assumed to have no effect on mortality risk, given no impact upon mortality was observed in SELECT-GCA. Instead, the model applies a GCA-specific mortality risk that varies over time. Mortality was determined by general population all-cause mortality rates, adjusted for excess mortality associated with GCA.^{104,130} Specifically, for patients experiencing any flare during the first year, a short-term standardised mortality ratio (SMR) is applied to reflect the higher early mortality risk¹⁰⁴; After the first year, a separate, lower SMR is used to capture the overall long-term GCA-related excess mortality.¹⁰⁴ In each model cycle, death is assumed to occur with equal probability from any health state (except where increased mortality is linked to certain adverse events [Section 3.3.1.3]).

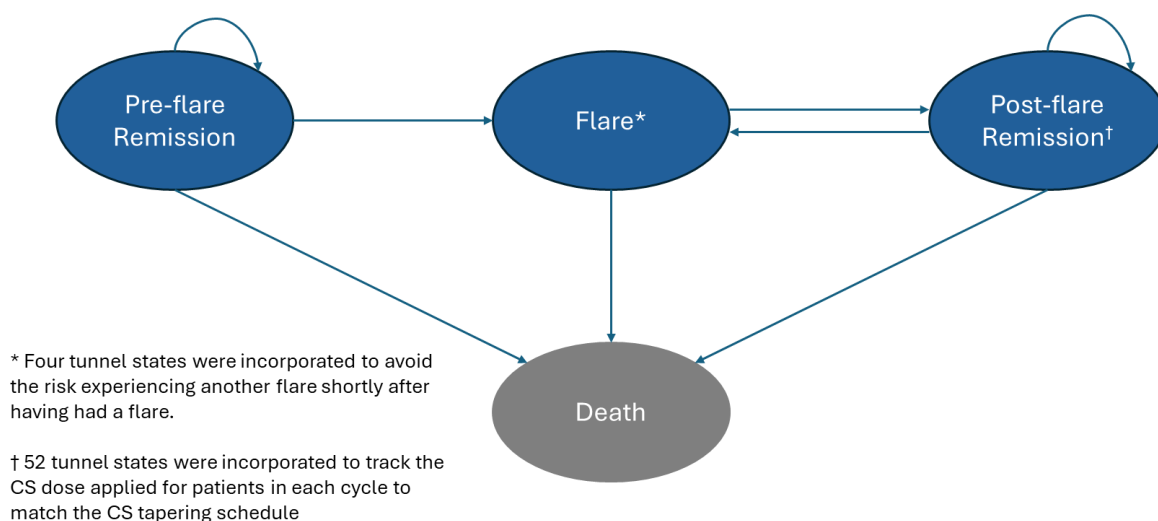


Figure 11. Model state transition structure

The key features of the CEA in comparison with previous appraisals in GCA are summarised in Table 23.

Table 23. Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
	TA518	Chosen values	Justification
Model structure	Semi-Markov Model	Semi-Markov model	In line with TA518, a semi-Markov model is able to follow patients through flare events and track them during corresponding tapering schedules, thereby appropriately capturing the clinical pathway in GCA.
Time horizon	Lifetime	Lifetime	To comprehensively capture all relevant differences in costs and benefits between treatments and the potential lifelong consequences of complications and adverse events.
Cycle length	Weekly (7 days)	Weekly (7 days)	In line with corticosteroid tapering schedule

Half-cycle correction	No half-cycle correction applied	No half-cycle correction applied	7-day cycle length is considered sufficiently short to capture changes to patient outcomes
Treatment waning	Treatment benefits continued over a lifetime	Treatment benefits end following treatment.	In line with preferred assumption by EAG in TA518.
Source of utilities	Health-state utilities from the GiACTA trial and subsequent data analysis, plus GCA-relevant published literature.	Health-state utilities from the SELECT-GCA and subsequent data analysis	Consistent with the NICE reference case. Health state utilities derived from GiACTA (aligned to TA518) are explored in scenario analyses
Source of costs	Drug costs from Dictionary of Medicine and Devices. NHS unit costs from PSSRU 2016 and Reference Cost Collection 2015. GCA-related complication costs and GC-related AE costs taken from relevant literature.	Drug costs from BNF and eMIT. NHS unit costs from Reference Cost Collection 2023/24 and PSSRU 2023. GCA-related complication costs and GC-related AE costs taken from relevant literature.	Consistent with the NICE reference case
Health effect measures	QALYs, EQ-5D-3L from GiACTA	QALYs, EQ-5D-5L from SELECT-GCA (mapped to 3L)	Consistent with the NICE reference case
Discount rate	Annual rate of 3.5% to both costs and QALYs	Annual rate of 3.5% to both costs and QALYs	Consistent with the NICE reference case
Perspective	UK National Health Service (NHS) and Personal Social Services (PSSRU)	UK National Health Service (NHS) and Personal Social Services	Consistent with the NICE reference case

Abbreviations: BNF, British National Formulary; eMIT, drugs and pharmaceuticals electronic market information tool; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services research Unit; QALY, quality-adjusted life year; TA, technology appraisal

Pairwise ICERs for upadacitinib vs. placebo are reported to evaluate cost-effectiveness. Additionally, QALY shortfall, defined as the absolute and relative differences between GCA patients and the general population, and net health benefit (NHB) are evaluated.

3.2.3 Intervention technology and comparators

As described in Section 3.2.3, the intervention of interest in this CEA is upadacitinib, administered orally as a 15 mg daily dose. The dosing regimen is detailed in Table 24. The relevant comparator for all patients with GCA in this appraisal are corticosteroids, which is modelled based on the dosing regimen used in SELECT-GCA.

Emerging evidence indicates that treatment with an active agent beyond one year is often necessary to maintain disease control and prevent relapse.²⁸ Reflecting this and in line with clinical feedback, the base-case analysis assumes a 24-month treatment duration for upadacitinib.

Recognising that a substantial proportion of patients may require a flexible treatment duration therapy beyond this period, alternative durations—including 3-year, 5-year, 10-year, and lifetime treatment—were explored through scenario analyses. This approach is consistent with the draft SmPC, which states that treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient preference.

The CEA includes the following intervention and comparators:

- Upadacitinib 15 mg OD + 26-week corticosteroid tapering
- 52-week corticosteroid tapering

The dosing regimens were modelled based on the corticosteroid tapering protocols used in SELECT-GCA (Appendix J). This aligns with recommendations from the EULAR and BSR guidelines.

Table 24. Intervention and comparator dosing schedules

Treatment	Dosing schedule	corticosteroid tapering
Upadacitinib (intervention)	15 mg OD	Prednisone/prednisolone as per tapering schedule for 26 weeks with the oral dose at 20, 30, 40, 50, or 60 mg OD

Treatment	Dosing schedule	corticosteroid tapering
Corticosteroid (comparator)	1 tablet OD	Prednisone/prednisolone as per tapering schedule for 52 weeks with the oral dose at 20, 30, 40, 50, or 60 mg OD

Abbreviations: corticosteroid, corticosteroid; OD, daily

3.3 Clinical parameters and variables

The following clinical parameters for the model are derived from the 52-week data of the pivotal SELECT-GCA trial: TTFF; subsequent flare rate; cumulative steroid dose; utility on flare; and utility on remission.

Given the 52-week duration of the SELECT-GCA trial, additional data sources were required to supplement trial data to effectively model the cost-effectiveness of upadacitinib over a life lifetime horizon, as per NICE reference case requirements. This included using a real-world evidence (RWE) study to inform rates of AEs, rather than relying on the short-term nature of corticosteroid related AEs observed in the trial (Section 3.3.2.2). A similar approach to deriving corticosteroid related AEs from RWE was considered appropriate in TA518 given limited AE observations from short term clinical trials. In addition, rates of GCA-related AEs were informed by published literature. All assumptions and sources were validated with clinical experts during the advisory board discussions, ensuring alignment with real-world clinical experience and contemporary practice. Additionally, mortality data collected from existing literature and national statistics were used to reflect the real-world risk of mortality for patients with GCA where this was not observed in SELECT-GCA.

3.3.1 Transition probabilities

The transition probabilities used in the model and the data sources are summarised below in Table 25 and are discussed in more detail in the following sections.

Table 25. Health state transitions

Transition	Transition probability	Source
Pre-flare remission to flare	Time dependent, calculated from the phase 3 clinical trial data of the TTFF	SELECT-GCA trial ²¹

Transition	Transition probability	Source
Flare to post-flare remission	All patients stay in flare state for 4 weeks and transition to post-flare remission	Based on committee preferred assumptions in TA518 and validated at advisory board.
Post-flare remission to flare (subsequent flare)	Constant rates, calculated from phase 3 clinical trial data	SELECT-GCA trial ²¹
Death from any state	No deaths occurred during the SELECT-GCA; mortality rates are linked to national statistics and rates from published GCA literature	National statistics ¹³⁰ , Therkildsen 2022 ¹⁰⁴

Abbreviations: GCA: giant cell arteritis; TTFF: time to first flare

3.3.1.1 Time to first flare

Time to first flare (TTFF) was defined as time from achieving remission to first disease flare. Disease flare in the SELECT-GCA trial was defined as an event determined by the investigator to represent recurrence of GCA signs or symptoms or an erythrocyte sedimentation rate (ESR) measurement > 30 mm/hr attributable to GCA and requiring an increase in corticosteroid dose. Patients who never achieved remission during the trial period were censored at Day 1.

In SELECT-GCA, TTFF was observed over a 52-week period. However, because the CEA applies a lifetime horizon, simple parametric models were applied to the Kaplan-Meier (KM) curves to extrapolate TTFF beyond the 52-week observed period. This approach allows the long-term risk of relapse to be captured and ensures that the differences in relapse profiles and associated corticosteroid dosing are adequately reflected throughout a patient's lifetime.

Different parametric models were tested, and the goodness of fit assessment was based on both the statistical index of Akaike Information Criterion (AIC) and visual inspection. Models with an AIC difference of ≤ 2 were considered statistically comparable.

Table 26 summarises the AIC values for various parametric models fitted to the TTFF data. For the upadacitinib arm, the generalised gamma distribution achieved the lowest AIC, with the log-normal model providing a comparable fit. In contrast, all

other models were more than 2 points higher, indicating an inferior fit for the upadacitinib arm.

For the corticosteroid arm, the log-normal distribution delivered the lowest AIC, whilst the generalised gamma and exponential distributions offered a comparable fit. Similar to upadacitinib, all other distributions were more than 2 points higher, indicating an inferior fit.

Table 26. AIC for parameter fit on time to first flare

Transition	UPA + 26 WK CS-T	PBO + 52 WK CS-T
Exponential	624.450	473.632
Weibull	626.310	475.621
Log-logistic	624.569	474.503
Log-normal	620.788	472.087
Gompertz	623.643	475.245
Gamma	626.417	475.629
Generalised Gamma	619.353	473.286

Abbreviations: AIC, Akaike Information Criterion; CS-T, corticosteroid tapering; PBO, placebo; UPA, upadacitinib, WK, week

The extrapolations were further validated through clinician consultation to confirm whether the long-term flare predictions generated by the model were clinically reasonable and aligned with expectations for real-world disease progression. This approach is consistent with best practice as outlined in emerging frameworks for assessing clinical plausibility of survival extrapolations.¹³¹

Figure 12 and Figure 13 present the observed and predicted TTFF for upadacitinib + 26-week corticosteroid tapering, and 52-week corticosteroid tapering arms in the trial population. Clinical experts confirmed that the proportion of GCA patients treated with corticosteroid tapering alone remaining flare free over time aligns with clinical observations. They supported the use of the log-normal curve for extrapolating TTFF for the corticosteroid tapering comparator. For upadacitinib, the log-normal curve was also selected for the base-case extrapolation, reflecting clinician feedback that this profile was consistent with expected flare rates if treatment were continued beyond the 52-week trial period.

Under the log-normal extrapolation, approximately 46% and 35% of patients treated with upadacitinib were predicted to remain flare-free at 3 and 5 years, respectively. This was 25% and 15% for the corticosteroid tapering arm at 3 and 5 years, respectively. These values were considered clinically plausible and reflective of long-term disease control observed in practice. The generalised gamma distribution was explored as a scenario analysis, which predicts a higher proportion of patients remaining flare-free (56% at 3 years and 50% at 5 years). Clinical opinion indicated that the base-case log-normal extrapolation was more realistic than the generalised gamma scenario, which could be an overestimate of long-term disease control. The parametric models selected for the base case analysis are shown in Table 27.

Figure 12. Parametric extrapolation of TTFF for UPA + 26-week corticosteroid tapering

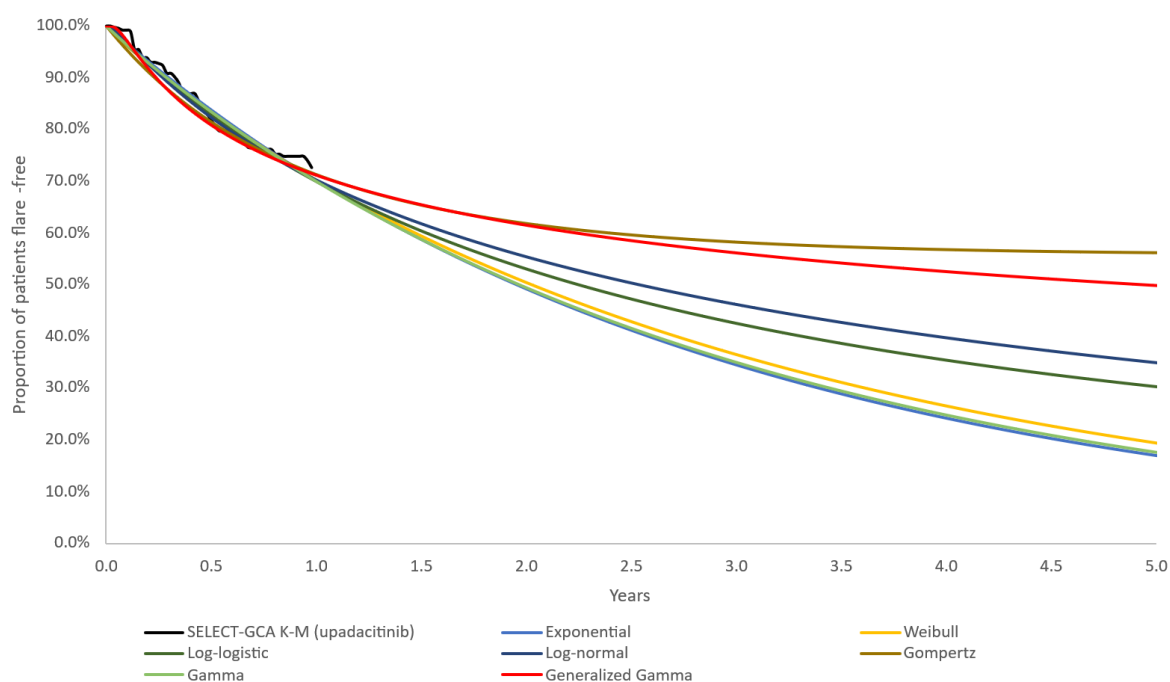


Figure 13. Parametric extrapolation of TTFF for PBO + 52-week corticosteroid tapering

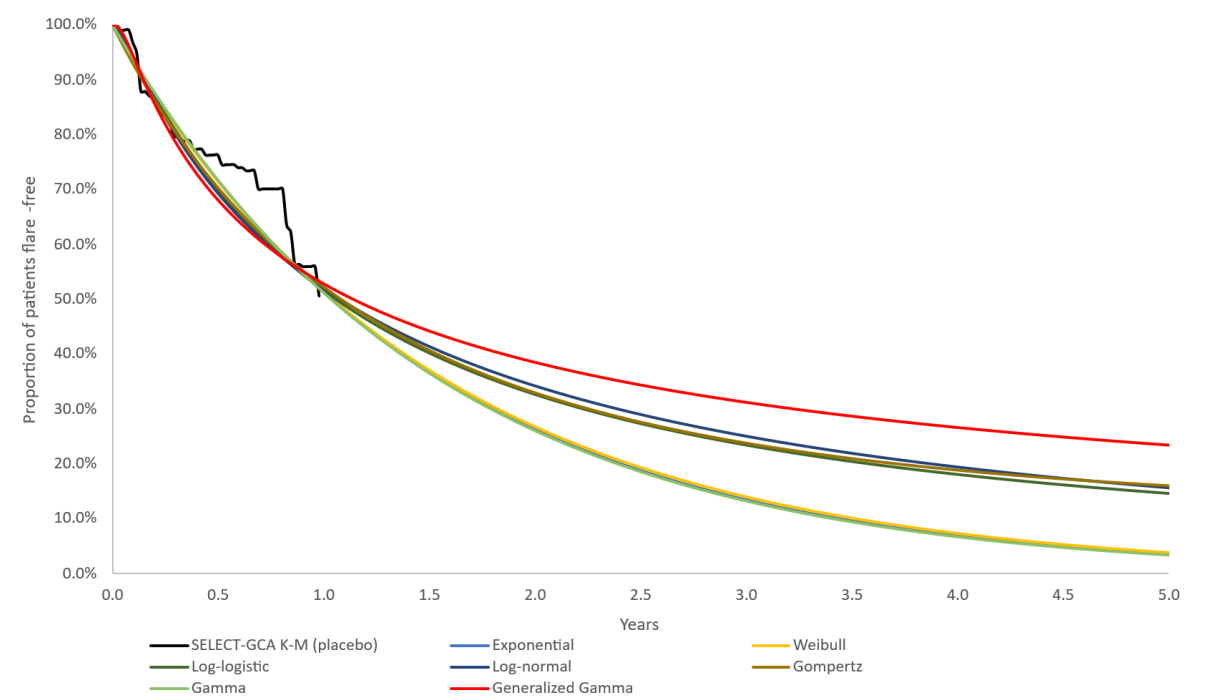


Table 27. Distributions for base case analysis

UPA + 26 WK CS-T	PBO + 52 WK CS-T
Log-normal	Log-normal

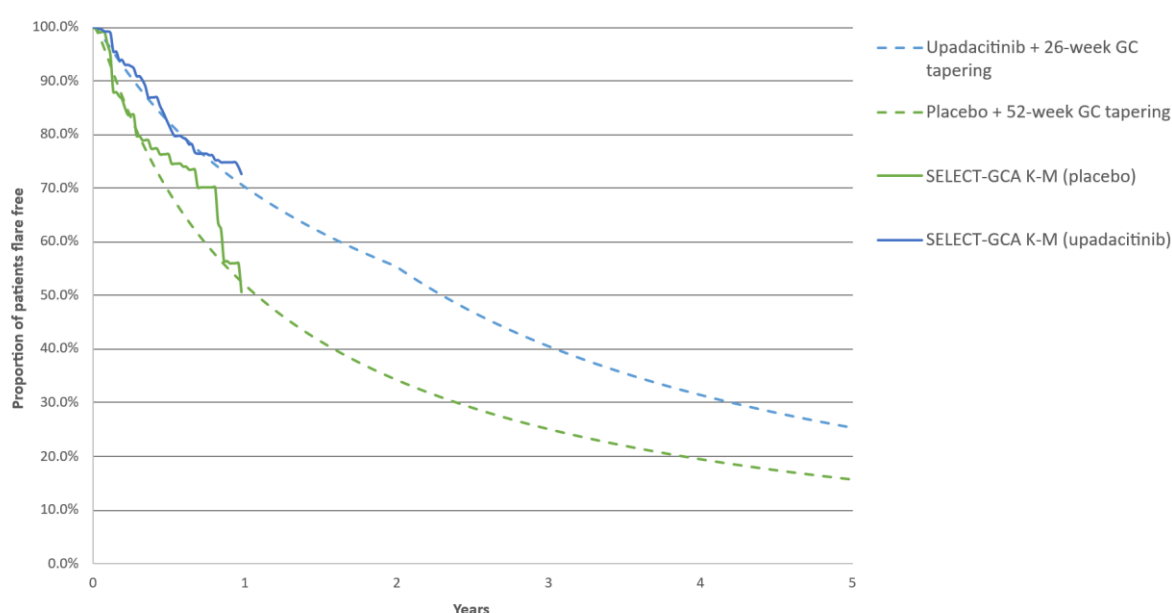
Abbreviations: CS-T, corticosteroid tapering; PBO, placebo; UPA, upadacitinib, WK, week

To reflect changes in treatment effectiveness following cessation of upadacitinib, a piecewise extrapolation approach is applied to model TTFF. In the base-case analysis, patients treated with upadacitinib are assumed to experience a shift in flare probability to that of the placebo (corticosteroid tapering) group immediately after completing treatment (2 years). This is implemented by switching the probability of first flare—rather than the survival curve itself—to match that of the comparator, resulting in a step change in flare risk post-treatment.

To explore a more gradual loss of efficacy after stopping treatment, scenario analyses apply a waning period during which the probability of flare for upadacitinib

patients linearly converges towards that of the placebo arm. In addition, a scenario assuming no loss in treatment efficacy after stopping upadacitinib is also explored — this assumption is consistent with the approach taken in TA518, where no treatment waning was applied following discontinuation of tocilizumab. This approach of considering different scenarios allows the impact on the ICER to be assessed under alternative but clinically plausible assumptions regarding the durability of treatment effect, particularly as it relates to decisions around the appropriate stopping point for upadacitinib. The KM curves for each treatment arm and selected base case parametric models are presented in Figure 14.

Figure 14. Parametric extrapolation of TTFF



3.3.1.2 Time to subsequent flare

The weekly rates of subsequent flare for the upadacitinib + 26-week corticosteroid tapering arm and placebo + 52-week corticosteroid tapering arm were estimated from SELECT-GCA data,²¹ using a Poisson regression — selected as appropriate for modelling count data over a defined exposure period. 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 to derive the number of subsequent flares within the trial period. The

rates were converted to weekly transition probabilities to fit the model cycle of 7 days. The weekly rates and probability of subsequent flares for are shown Table 28.

Table 28. Weekly rate of subsequent flare in each treatment arm

Treatment arm	Weekly rate of subsequent flare		Weekly probability of subsequent flare (mean)
	Mean	95% CI	
UPA + 26 WK CS-T	0.0069	(0.0037, 0.0129)	0.0069
PBO + 52 WK CS-T	0.0114	(0.0066, 0.0165)	0.0113

Abbreviations: CI, confidence interval; CS-T, corticosteroid tapering; PBO, placebo; UPA, upadacitinib, WK, week

The base-case analysis assumes a constant weekly rate of subsequent flares over time for both treatment arms. The base case assumption of a constant rate of subsequent flares is supported by published evidence and clinical validation (as noted by cumulative flare estimates below). This approach also responds to concerns raised in TA518 regarding the potential overestimation of flare rates. In TA518, the model predicted a mean of 19.67 flares over a 30-year period for the corticosteroid comparator. The EAG noted that, based on a median 10-year follow-up, Proven et al. (2003) observed a maximum of 7 flares per patient,²⁶ while Larbaca et al. (2015) reported a median relapse rate of 0.4 relapses per year—roughly 2 flares over 5 years.³⁵ These published estimates suggest that their model’s predictions, which equate to about 10 relapses over 10 years (or roughly one flare per year), substantially overestimated the number of subsequent flares. In contrast, the current model estimates of the cumulative number of predictive flares over 5- and 10- years are well aligned with the literature – as shown in Table 29.

Table 29. Model-predicted cumulative flares by treatment arm

Treatment arm	Cumulative flares (per-patient) 5-year horizon	Cumulative flares (per-patient) 10-year horizon
UPA + 26 WK CS-T	1.8356	3.7774
PBO + 52 WK CS-T	2.4220	4.4625

To strengthen the external validity, model predicted cumulative flares were further validated during advisory board discussions to ensure the model’s long-term

predictions were realistic and as expected in contemporary clinical practice. Nonetheless, in comparison with the literature, the number of flares estimated for the placebo arm could be considered conservative and thus the results could be underestimating the benefits of upadacitinib.

Nevertheless, acknowledging that a proportion of patients may experience fewer flares over time with successful disease management, scenario analyses were conducted to explore alternative assumptions. These included annual reductions of 5% and 10% in the flare rate to reflect the potential decline in flare risk associated with effective long-term treatment (Section 3.11.4).

3.3.1.3 Mortality

The model incorporates background mortality for all patients based on UK lifetables (Office of National Statistics 2020-2022).¹³⁰ The model also captures excess mortality in GCA using three components:

- Short-term excess mortality associated with flare
- Long-term disease-specific mortality risk
- AE-related mortality risk (accounted for indirectly via disutilities and costs)

Patients from all health states were subject to a mortality similar to those of the general population, with a short-term and long-term relative risk (RR) applied for disease-specific mortality linked to GCA.

Short-term mortality during flare

For patients experiencing flare, the model applies an elevated mortality risk during the first year to capture the additional burden associated with GCA complications. Published evidence indicates that GCA patients face a higher risk of death in the first year, so an SMR of 1.49 is applied during this period to account for the elevated risk.¹⁰⁴

Long-term excess mortality from GCA

After the first year, the model reverts to the lower RR of 1.03 to reflect the long-term excess mortality risk in GCA patients. This estimate is based on a study assessing long-term survival in patients with GCA.¹⁰⁴ Disease-specific mortality in GCA includes an increased risk of death due to infectious diseases, endocrine disorders, cardiovascular complications, and gastrointestinal conditions, likely influenced by the long-term use of glucocorticoids and the systemic effects of vascular inflammation.

Although the source of the long-term relative risk is based on a 10-year mortality comparison, the model applies the RR to weekly probabilities of death derived from annual UK lifetable mortality rates. This simplification was necessary due to the structure of the lifetables, which report mortality up to age 100 only. As a result, calculating 10-year mortality probabilities for patients aged 91 and above is not feasible, and becomes increasingly unreliable in the oldest age groups (e.g., age 99, where only a single year is available). Applying the RR directly to weekly mortality rates allows for consistent and feasible implementation across all ages, while acknowledging a potential minor overestimation in younger age groups. This approach represents a pragmatic modelling decision and alternative approaches were shown not to impact cost-effectiveness results.

Adverse event-related mortality

In addition to flare-related mortality, patients who experience certain adverse events with long-term consequences (such as cardiovascular events, major stroke, or other complications deemed lifelong in the model) are assumed to face a persistently elevated mortality risk. However, the model does not explicitly assign additional cause-specific mortality transitions for each AE. Instead, a conservative simplifying assumption is applied: the long-term RR of 1.03 is assumed to account for the cumulative excess mortality risk across all such lifelong AEs. As such, AE-related mortality is indirectly incorporated through ongoing utility decrements and event costs, with the RR approach serving to conservatively capture associated long-term risk in a feasible and transparent way. While this approach underestimates the

elevated short-term mortality risk (hazard ratio of 1.49) immediately following an event¹⁰⁴, implementing a time-varying risk would require the use of tunnel states for each life-long AE, adding significant complexity to the model. This level of structural refinement was deemed impractical and unlikely to meaningfully affect outcomes. Therefore, the chosen approach represents a conservative and pragmatic simplification that aligns with the expected direction of effect while maintaining model transparency.

3.3.2 Corticosteroid dose

3.3.2.1 Cumulative GC dose

SELECT-GCA demonstrated that upadacitinib provides a statistically significant and clinically meaningful steroid-sparing effect in individuals with GCA.²¹ Upadacitinib's ability to reduce the required dose of corticosteroids whilst preventing GCA relapse or flare is particularly important as both high-dose and long-term corticosteroid use (cumulative AE exposure) are associated with serious AEs (Section 3.3.2.2). The model therefore included the steroid-sparing effect of treatment by extrapolating the corticosteroid dose received for patients in each treatment arm.

High doses of corticosteroid therapy are initially required and provide rapid control of inflammation, preventing vision loss and other irreversible complications.^{2,3} Initial high dose corticosteroid therapy is followed by a prolonged period of dose tapering in clinical practice and reflected in SELECT-GCA (Appendix J).^{22,91} Aligned to the SELECT-GCA protocol, it is assumed that patients experiencing a flare would switch to the corticosteroid tapering regimen based on the investigating clinician's judgment.²² In the base case analysis, patients are maintained on the last effective dose (pre-flare) until the flare is resolved. One week after they return to the remission state, their corticosteroid tapering regimen is resumed from last effective dose.

Clinicians consulted during the advisory board suggested that some patients may experience a severe flare, which require retreatment with corticosteroid at an elevated dose, higher than their last effective dose pre-flare. Clinical experts

considered that approximately 20% of flares will be severe in the overall GCA population. Furthermore, the TOCSTOP study reported outcomes from a cohort of relapsing and refractory GCA patients, reporting that 33.6% of relapses were severe (as defined by EULAR criteria).²⁸ To reflect these observations, the base-case CEA assumed that 20% of patients who flared experienced a 'severe' flare, and restarted corticosteroid at a dose of 40mg. Scenario analyses were conducted to explore the impact of no patients experiencing a severe flare, as well as a scenario where patients restarted at the highest dose of corticosteroid received at SELECT-GCA baseline (60mg).

The model estimated the cumulative corticosteroid dose for patients in each treatment group accordingly in three stages:

- Pre-flare remission: patients received upadacitinib during their pre-flare remission and followed the 26-week corticosteroid tapering – as defined in the SELECT-GCA protocols.^{22,91} Similarly, patients in the placebo arm, followed the 52-week corticosteroid tapering as specified in the SELECT-GCA protocol.²²
- Flare: when patients entered the flare state, the corticosteroid dose depended on the flare severity. For minor flares, they were treated with the last effective dose for 4 weeks until remission was achieved. For severe flares, patients restarted at 40 mg corticosteroid for four weeks until remission was achieved. The last effective dose was determined by the daily corticosteroid dose in the previous cycle, while in the pre-flare remission state (e.g., when a patient experienced disease flare while on 30 mg daily dose, the last effective dose was 35 mg).
- Post-flare remission: after achieving remission following 4 weeks in the flare state, patients maintained their corticosteroid dose in the flare state for 1 week and then resumed tapering as per SELECT-GCA protocol.

To calculate cumulative corticosteroid exposure, the model followed a stepwise approach that accounted for dynamic treatment progression/exposure over time.

First, the average daily corticosteroid dose was calculated for each health state. Then, the dose was weighted by the proportion of patients in that state during each model cycle. Finally, the cumulative corticosteroid dose was determined by summing the current cycle’s weighted dose with the cumulative total from all previous cycles. This rolling calculation allowed the model to accurately reflect dose accumulation over time, both during and beyond the 52-week trial period.

The predicted cumulative corticosteroid dose for each treatment arm during the trial period (52 weeks) and lifetime horizon can be found in Table 30

Table 30. Predicted cumulative corticosteroid exposure

Treatment arm	Cumulative corticosteroid doses (mg)	
	52 weeks	Lifetime horizon (28.9 years)
UPA + 26 WK CS-T	1,893.08	8.710.05
PBO + 52 WK CS-T	3,513.79	18,018.35

Abbreviations: CS-T, corticosteroid tapering; mg, milligram; PBO, placebo; UPA, upadacitinib, WK, week

3.3.2.2 *Corticosteroid-related AEs associated with cumulative corticosteroid burden*

Corticosteroids are the current main treatment for patients with GCA, with high-dose and long-term use being closely linked to serious adverse events.

Corticosteroid-related AEs were specifically modelled to capture the benefits of steroid-sparing regimens. Patients with GCA were at risk of developing corticosteroid-related AEs during steroid tapering, disease flare and post-flare remission. Corresponding utility decrements and costs were applied. Details of corticosteroid dose applied in the model are discussed in Section 3.3.2.1.

Observed overall AE rates and corticosteroid-related AEs specifically in SELECT-GCA were low,^{21,91} likely due the long-term nature of these AEs, the controlled environment, and the relatively short follow-up period (52-weeks); thus, underestimating the long-term risk imposed by corticosteroid exposure. To address this, AE rates were derived from an external RWE study using IBM Watson Health MarketScan Commercial and Medicare databases.⁴⁴ This 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), thereby providing a more robust and representative record of the cumulative and variable risks associated with long-term corticosteroid exposure compared to shorter term clinical trial observations.

Advisory board discussions provided strong agreement with this approach in order to capture the burden of cumulative corticosteroid exposure upon patients. Clinical experts noted that short-term clinical trials fail to adequately capture the long-term burden of corticosteroid-related AEs—such as increased cardiovascular risk, osteoporosis, and hypertension—which are inherently dose-dependent and cumulative. Moreover, despite the RWE study being US-based and predominantly recruiting new-onset GCA patients, its population characteristics (e.g., 55.6% aged ≥ 70 , 68.8% female, and 98.1% receiving prednisone) were considered broadly reflective of UK practice. Clinical experts also reviewed and agreed that the specific corticosteroid related AEs captured in the study and subsequently incorporated into the CEA were appropriate and reflecting those of most clinical significance; specific AE durations applied in the CEA were also validated and aligned to clinical expert feedback. It is also noted that the derivation of corticosteroid AE rates and associated cumulative dose from RWE is aligned to the approach accepted during TA518, where similarly, due to limitations of the short-term clinical trial, corticosteroid related AE rates were low and not considered reflective of clinical practice.

Patients were stratified by their average daily corticosteroid dose into four groups: low dose (≤ 5 mg), medium dose (> 5 mg to ≤ 10 mg), high dose (> 10 mg to ≤ 20 mg), very high dose (> 20 mg to ≤ 40 mg), and extremely high dose (> 40 mg). Although the study's dose thresholds were originally based on average annual doses, in the model patients incur AEs according to these thresholds at each cycle. For example, while a patient's cumulative corticosteroid dose is below 1,826 mg, they are assigned the low-dose AE rates; when their cumulative dose is between 1,826 mg and 3,653 mg, medium-dose AE rates are applied; a cumulative dose between 3,653 mg and 7,305 mg triggers high-dose AE rates; a cumulative dose between 7,305 mg and 14,610

triggers very high-dose AE rates, and exposure beyond 14,610 mg results in extremely high-dose AE rates.

Given patients enrolled in the RWE study had new-onset GCA, it is assumed in the CEA that all patients have the same cumulative corticosteroid dose, which is considered a conservative assumption as patients with relapse would likely have a higher corticosteroid burden at the point of relapse in clinical practice and be at a higher risk of related AEs. Clinicians consulted at the advisory board also contributed to defining the corticosteroid dose thresholds applied for low dose corticosteroid, medium dose etc., suggesting that the brackets (0–5 mg, 5–10 mg, 10–20 mg, 20–40 mg and >40 mg) are appropriate and reflective of their observations of steroid burden differentiation in UK clinical practice.

Further validation of the RWE approach was conducted through clinical consultation. Three HCPs reviewed the incidence rates of adverse events observed in the RWE study, comparing them against trial observations and published literature. The clinicians confirmed that the incidence estimates used in the model were clinically plausible and aligned with expectations in real-world settings. Additionally, the set of AEs included in the analysis was further reviewed and validated as appropriately capturing those AEs considered to be causally linked to long-term steroid exposure with the durations of each AE applied in the CEA considered appropriate. A summary of the corticosteroid-related AE rates derived from the RWE study is provided in Table 31.

By mapping cumulative corticosteroid dose data from SELECT-GCA to AE rates from the MarketScan RWE study, the CEA more accurately reflects the increasing risk of AEs as corticosteroid exposure accumulates, providing a clinically relevant and externally validated basis for evaluating the steroid-sparing benefits of treatment. It should also be noted that corticosteroid-related AEs are under-reported, and certain long-term complications may not be fully captured in trial datasets. As such, this approach is likely to represent a conservative estimate of the true burden of steroid-related harm.

Table 31. Annual rates of CS-related AE

AE rates	Low dose (0-5 mg)	Medium dose (5-10 mg)	High dose (10-20 mg)	Very High Dose (20-40 mg)	Extremely High Dose (>40 mg)
Metabolic Events					
Increased BMI	■	■	■	■	■
Pre-diabetes	■	■	■	■	■
Type 2 diabetes	■	■	■	■	■
Hyperlipidemia	■	■	■	■	■
Endocrine adrenal insufficiency	■	■	■	■	■
Cushing's syndrome	■	■	■	■	■
Cardiovascular Events					
Hypertension	■	■	■	■	■
Electrolytes (sodium, potassium) abnormalities	■	■	■	■	■
Heart failure	■	■	■	■	■
Atherosclerosis	■	■	■	■	■
Palpitations	■	■	■	■	■
Musculoskeletal Events					
Myopathy	■	■	■	■	■
Aseptic necrosis of bone	■	■	■	■	■
Tendon rupture	■	■	■	■	■
Bone Density Events					
Osteoporosis	■	■	■	■	■
Non-traumatic fracture	■	■	■	■	■
Gastrointestinal Events					
GI perforation	■	■	■	■	■
Ulcer/GI bleed	■	■	■	■	■
Gastritis	■	■	■	■	■
Psychiatric Events					

AE rates	Low dose (0-5 mg)	Medium dose (5-10 mg)	High dose (10-20 mg)	Very High Dose (20-40 mg)	Extremely High Dose (>40 mg)
Anxiety, depression, mania, hyperactivity, psychosis, or delirium	■	■	■	■	■
Infection events					
Opportunistic infections	■	■	■	■	■
Sepsis	■	■	■	■	■
Severe infection: hospitalizations	■	■	■	■	■
Ocular Events					
Cataract	■	■	■	■	■
Glaucoma	■	■	■	■	■
Increased IOP	■	■	■	■	■
Sleep Disorders					
Sleep disorders	■	■	■	■	■
Dyspnea	■	■	■	■	■
Skin Events					
Bruising	■	■	■	■	■
Skin thinning	■	■	■	■	■
Impaired wound healing	■	■	■	■	■
Acne	■	■	■	■	■
Others					
Hirsutism	■	■	■	■	■

Abbreviations: AE, adverse event; BMI, body mass index; GC, glucocorticoids; IOP, intraocular pressure

To address uncertainty around the specific corticosteroid-related AEs included in the analysis, a scenario was conducted (section 3.11.4) applying only the corticosteroid-related AEs included in TA518 (i.e., fractures, diabetes, osteoporosis and infections).

3.3.2.3 Risk of GCA complications

GCA-related complications are experienced by a proportion of patients in the flare state. Since these serious complications are rare and were not observed during SELECT-GCA,^{21,91} the risks were derived from literature and converted to weekly probabilities in line with the model cycle length (Table 32).

Based on the available literature and clinical opinion the following complications were considered the most serious events related to flare which would impact upon patients HRQoL and are applied in the base case analysis. For the purposes of the model, patients are only at risk of experiencing GCA related complications whilst in the flare health state.

Table 32. Probability of CS-related complications

GCA-related complications	Weekly Probability of event	Reference
Vision loss (bilateral)	0.0003	Yates et al 2017 ¹³²
Vision loss (unilateral)	0.0031	
Aortic aneurysm	0.0002	Nuenninghoff et al 2003 ¹³³
Aortic dissection	0.0001	
Myocardial infarction	0.0007	Amiri et al 2015 ⁹⁹
Major stroke	0.0028	Gonzalez-Gay et al 2009 ¹³⁴
Minor stroke	0.0042	

Abbreviations: GCA, giant cell arteritis

3.3.2.4 JAK inhibitor-related AEs

In consideration of broader safety concerns around the JAKi drug class, known AEs associated with JAKi use (i.e., major adverse cardiovascular events [MACE] and venous thromboembolism [VTE]) were incorporated into the CEA for patients in the upadacitinib + 26-week corticosteroid tapering arm. Patients were at risk to develop JAKi-related AEs in the model whilst actively receiving upadacitinib. Since these AEs are rare and did not occur during the SELECT-GCA trial,²¹ the risks were derived

from a compilation of SELECT studies by Cohen et al.,¹³⁵ and were converted to weekly probabilities in line with the model cycle length (Table 33).

Table 33. JAKi-related AE rates

JAKi-related AEs	Probability	Source
MACE	0.0001	Cohen et al. (2021) ¹³⁵
VTE	0.0001	

Abbreviations: AE, adverse event; JAKi, Janus kinase inhibitors; MACE, major adverse cardiovascular events; VTE, venous thromboembolism

3.3.3 Treatment duration

Clinical experts consulted at the advisory board emphasised that considering the extended follow up data post-tocilizumab discontinuation (TOCSTOP) and observations in UK practice, a substantial proportion of patients relapse in the short-term following treatment discontinuation; thus, there is a clinical need for a corticosteroid sparing therapy with flexible duration for patients with GCA in contemporary practice. Clinicians indicated that patients are expected to benefit from upadacitinib beyond the initial treatment period observed in SELECT-GCA (52-weeks). Moreover, it was noted that a subset of patients may require long-term or even lifelong continuous treatment to maintain disease control. Clinical insight underscores the unmet need for flexible treatment durations, particularly among patients with moderate- to low-grade refractory disease.

Reflecting this, the base-case analysis assumed a treatment duration of 2 years, while scenario analyses explored the cost-effectiveness of upadacitinib over longer treatment durations of 3, 5, and 10 years, as well as a lifetime horizon. These treatment duration scenarios are justified not only by clinical observations and real-world unmet need for less restrictive prescribing of corticosteroid sparing therapy but also highlighted during advisory board discussion and echoed by consultees of the NICE scope, which emphasised the urgent need for a therapy with flexible treatment duration.

This approach demonstrates the cost-effectiveness of upadacitinib over different treatment durations, allowing a tailored treatment duration that considers patient preference and clinician judgement guided by disease activity.

Steroid tapering schedules in the model are aligned with those observed in SELECT-GCA,^{21,91} with a 52-week taper assumed for patients on corticosteroid alone and a 26-week taper for those receiving upadacitinib.

3.3.4 Efficacy waning post treatment discontinuation

While on treatment, efficacy is assumed to remain constant—an assumption supported by feedback from clinical experts during advisory board discussions, who indicated that patients would be expected to maintain benefit while actively receiving upadacitinib. In the base case analysis, it is assumed that upon treatment cessation, the effectiveness of upadacitinib instantaneously switches to that of the comparator, reflecting standard corticosteroid dosing without the steroid-sparing benefit.

However, whilst extended follow up data for upadacitinib following discontinuation in GCA are not yet available, it is likely that the assumption of no durable benefit is overly conservative. To explore this uncertainty, alternative scenario analyses were conducted in which treatment benefits were assumed to continue throughout the time horizon even after treatment discontinuation, as well as a more gradual treatment waning applied after discontinuation (assuming a waning period of 1 year) – thereby capturing the potential decline in upadacitinib’s effect over time. This approach ensures that the model reflects both the immediate loss of benefit upon treatment cessation and the possibility that the favourable effects of upadacitinib may diminish gradually in clinical practice.

3.3.5 Adherence

The model assumed 100% adherence to all treatments, including full adherence to the pre-defined corticosteroid tapering schedules for each treatment arm. This assumption was endorsed as appropriate by clinical experts during the advisory board. Clinicians noted that in the absence of a flare, patients are generally expected

to follow their prescribed treatment and tapering regimens closely – arguing that any adherence issues typically seen with oral medications would similarly affect other treatments, such as subcutaneous administrations. Given the challenges in establishing a reliable relationship between adherence and flare occurrence with the currently available clinical trial data, it is considered an appropriate simplification to assume complete adherence.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life studies

In line with the NICE requirements, an SLR was conducted to identify studies reporting utility values relating to the treatment of GCA. A full description of SLR methodology and outcomes is provided in Appendix F and an overview provided below.

In brief, electronic databases (including Embase, Medline, PubMed and EconLit) were searched to retrieve studies from 2010 to 13 May 2024, and subsequently updated on 19 February 2025. Electronic database searches included abstracts indexed by the Northern Light database; conference proceedings between 2019 and April 2024 were also searched to identify health state utility and disutility data relating to patients with GCA, including from the International Vasculitis Workshop and BSR annual conference. In addition, searches were performed on the websites of HTA authorities as previously detailed in section 3.1.

Literature searches were designed applying a combined approach to identify evidence relating to economic evaluations, costs and healthcare resource utilisation, and health state utility studies. A PRISMA diagram for the original combined literature review (date-span 2010 to 10 May 2024) is previously presented in section 3.1 (Figure 10); of the 35 unique studies included in the original searches, five were eligible as part of the utility SLR inclusion criteria. An additional two eligible studies reporting relevant utility data were identified in the SLR update (Figure 15).

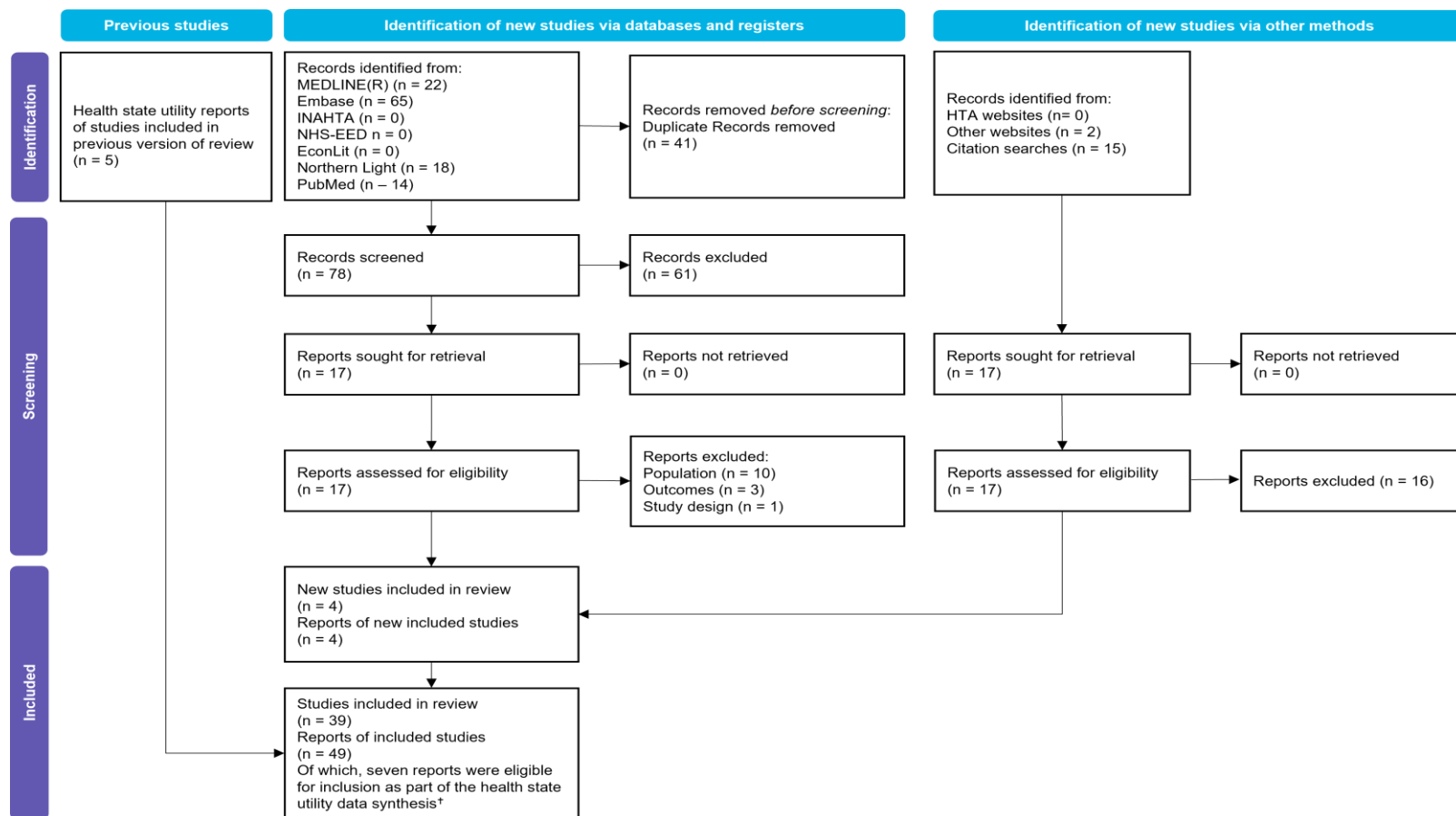


Figure 15. PRISMA diagram illustrating the study selection process for identifying health-related quality of life studies for the SLR update (searches to 18 February 2025)

The remaining 42 reports were eligible for inclusion as part of the cost-effectiveness evaluations review component and the cost and healthcare resource utilisation component, described in Appendix E and Appendix G, respectively.

Table 34. Utilities reported from GiACTA and informing health states for previous GCA appraisals

First Author (Year)	Population	Interventions/Comparators (N)	Instrument/Source	Health State Description	Utility/Disutility	
					Measure	Value
Strand (2019) ¹³⁶	Patients ≥ 50 years of age with newly diagnosed or relapsing active GCA	TCZ 162mg SC OW + 26w CS taper (85)	SF-6D	NR	Mean at baseline	0.694
				NR	Mean at week 52	0.775
		PBO + 26w CS taper (43)		NR	Mean at baseline	0.686
				NR	Mean at week 52	0.721
		PBO + 52w CS taper (45)		NR	Mean at baseline	0.663
				NR	Mean at week 52	0.692
Unizony (2021) ¹¹¹	GiACTA trial, patients with GCA responding to treatment	TCZ + CS (86)	EQ-5D	Responder	Mean (SD)	0.8 (0.2)
		PBO + CS (27)				0.8 (0.2)
	GiACTA trial, patients with GCA not responding to treatment	TCZ + CS (44)		Non-responder		0.7 (0.2)
		PBO + CS (67)				0.7 (0.2)

First Author (Year)	Population	Interventions/Comparators (N)	Instrument/Source	Health State Description	Utility/Disutility	
					Measure	Value
NICE TA518 (2018) ²⁷	Adults with GCA Overall	TCZ + 26w CS taper vs 52w CS taper (NA)	EQ-5D (UK Tariffs)	Remission	NR	0.7713
				Relapse/Flare		0.642
	Adults with GCA newly diagnosed	-		Remission		0.8115
		-		Relapse/Flare		0.6451
	Adults with GCA relapsing			Remission		0.7333
				Relapse/Flare		0.6343
CADTH (2018) ¹³⁷	Adults with GCA	TCZ + 26w CS taper vs 52w CS taper	EQ-5D-3L, based on GiACTA trial	Remission	NR	0.7713
				Flare		0.642

Abbreviations: CS: corticosteroids; GCA: giant cell arteritis; OD: daily; PBO: placebo; TCZ: tocilizumab

Of the included studies, five reported utility values derived from GiACTA or relating to the economic evaluation of tocilizumab, informed by GiACTA. Utility data derived from GiACTA were reported for EQ-5D (n=3) and SF-6D (n=1) instruments; values were reported across GCA sub-populations (new-onset and relapsing disease) and by disease status/health state (Table 34). Additionally, three of the economic evaluations included reported disutility values relating to AEs and corticosteroid related events (Appendix F).

3.4.2 Health-related quality-of-life data from clinical trials

The EQ-5D-5L questionnaire was administered to patients in SELECT-GCA at baseline, week 8, week 24, and week 52. In accordance with NICE's position statement on the EQ-5D-5L valuation set, patient responses to the EQ-5D-5L questionnaire were mapped onto the UK EQ-5D-3L value set using the crosswalk developed by van Hout et al. (2012).^{138,139}

Data from these evaluations were analysed to derive utility functions for implementation in the model. In line with the preferred approach from TA518, responses were pooled across placebo and upadacitinib 15 mg groups, as utilities are not considered treatment-dependent, and pooling provides a larger sample size and more robust estimates. Generalised linear mixed-effects models (with individual-level random effects) were used to account for the correlation among repeated measures for the same individual and health states (remission and flare), while baseline EQ-5D were considered as fixed effects in the model. This approach ensures that the derived utility estimates are both statistically robust and reflective of real-world patient experiences.

Utility values derived from SELECT-GCA data were used in the base-case analysis and are summarised in Table 35. The utility decrement between the flare and remission health states was estimated at -0.0587. Overall utility decrements between the flare and remission health states in SELECT-GCA are well aligned to previous observations from GiACTA, with a decrement of -0.13 for the overall GCA population (Table 36). Observed flare events in SELECT GCA were infrequent, and EQ-5D

evaluations were conducted at wider intervals during follow-up. As a result, while the utility data from SELECT-GCA reflect overall treatment experience, there may be limitations in capturing the short-term impact of acute flare episodes, particularly given the fast onset and transient nature of disease flares where the impact on quality of life is likely to be most pronounced. In the model, the flare-related utility decrement was applied during the 4-week flare period, using tunnel states to reflect this short-term impact with greater precision.

To explore the impact of more frequent HRQoL assessments, a scenario analysis was conducted using data from the GiACTA trial.²⁷ In GiACTA EQ-5D-3L data were collected at baseline and at weeks 12, 24, 36, and 48, potentially offering greater granularity in capturing utility changes during flares and remission. Although it may be considered that GiACTA faced similar challenges with frequency of HRQoL assessment, it also provides a more robust reflection of utility changes as there was a larger cohort (four treatment arms) from which utilities are derived and pooled in the analysis. The same statistical approach was applied to derive utility values, using a mixed effects model that adjusted for baseline utility and accounted for within-individual correlation. Utilities calculated from GiACTA are summarised in Table 36.

Table 35. Utilities from SELECT-GCA

Flare Status	Utility	Standard error	Lower 95% CI	Upper 95% CI
Flare	0.7098	0.0265	0.6580	0.7617
No flare (remission)	0.7685	0.0083	0.7523	0.7847

Table 36. Utilities from GiACTA (scenario)

Flare Status	Utility	Standard error	Lower 95% CI	Upper 95% CI
Flare	0.6420	0.0245	0.5940	0.6901
No flare/ remission	0.7713	0.0067	0.7582	0.7844

3.4.3 Mapping

As noted in Section 3.4.1, patient responses to the EQ-5D-5L questionnaire were mapped onto the UK EQ-5D-3L value set using the crosswalk developed by van Hout et al. (2012).¹³⁹

3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Although age-dependent disutility was expected to have minimal impact on incremental QALYs given the assumption of no treatment-specific effect on life expectancy it was applied within the base case analysis.

3.4.4.1 Disutility related to GCA complications

Patients with GCA were at risk of developing GCA complications during disease flare (“flare” state) and corresponding utility decrements were applied. Utility decrements were applied for all the GCA complications included in the model, including unilateral vision loss, bilateral vision loss, minor stroke, major stroke, aortic aneurysm, aortic dissection, and myocardial infarction. Estimates of the disutility due to GCA-related complications were derived from the literature (Table 37) and validated with UK clinical experts.

A distinction was made between transient and lifelong adverse events. For transient AEs, the disutility was applied only in the model cycle during which the event occurred—specifically to patients in the flare health state. In contrast, lifelong AEs were modelled as ongoing impairments: each cycle accounted for patients newly experiencing a lifelong AE, as well as those continuing to live with the condition from previous cycles (as well as accounting for long-term mortality). This distinction allowed the model to more accurately capture the short-term versus enduring impacts of serious complications associated with GCA.

Table 37. Disutilities of GCA complications

GCA-related complications	Disutility	Duration	Reference
Vision loss (bilateral)	-0.220	Life-long	Konig et al. 2004 ¹⁴⁰
Vision loss (unilateral)	-0.040	Life-long	
Aortic aneurysm	-0.054	Transient	Sullivan et al., 2011 ¹⁴¹
Aortic dissection	-0.129	Transient	Patel et al. 1999 ¹⁴²
Myocardial infarction	-0.063	Transient	Sullivan et al. 2011 ¹⁴¹
Old myocardial infarction	-0.037	Life-long	
Major stroke	-0.101	Life-long	
Minor stroke	-0.033	Life-long	

Abbreviations: GCA, giant cell arteritis

3.4.4.2 Disutility related to CS-related AEs

Disutilities were also considered for corticosteroid-related AEs, as described in Section 3.3.2.2. Estimates were sourced from the published literature wherever possible and validated during advisory board discussions with UK clinical experts (Table 38). As with GCA-related complications, corticosteroid-related AEs were classified as either transient or lifelong events and operationalised consistently: transient AEs were associated with one-time disutility applied in the cycle in which the event occurred, while lifelong AEs carried a sustained disutility applied in all subsequent cycles following onset.

Table 38. Disutilities of CS-related AEs

AEs	Disutility	Duration	Reference
Metabolic Events			
Increased BMI	-0.004	Transient	Sullivan et al., 2016 ¹⁴³
Pre-diabetes	-0.0335	Transient	TA924 (hypoglycaemic event) ¹⁴⁴

Type 2 diabetes	-0.0380	Transient	Søltøft et al., 2009 ¹⁴⁵
Hyperlipidemia	-0.0065	Life-long	Sullivan et al., 2011 ¹⁴¹
Endocrine adrenal insufficiency	-0.0303	Transient	Sullivan et al., 2011 ¹⁴¹
Cushing's syndrome	-0.0303	Transient	Sullivan et al., 2011 ¹⁴¹
Cardiovascular Events			
Hypertension	-0.046	Transient	Sullivan et al., 2011 ¹⁴¹
Electrolytes (sodium, potassium) abnormalities	-0.03	Transient	TA877 ¹⁴⁶
Heart failure	-0.1167	Life-long	Sullivan et al., 2011 ¹⁴¹
Atherosclerosis	-0.0364	Life-long	Sullivan et al., 2011 ¹⁴¹
Palpitations	-0.0384	Transient	Sullivan et al., 2011 ¹⁴¹
Musculoskeletal Events			
Myopathy	-0.05	Transient	TA518 ²⁷
Aseptic necrosis of bone	-0.06	Life-long	TA518 ²⁷
Tendon rupture	-0.15	Life-long	TA518 ²⁷
Bone Density Events			
Osteoporosis	-0.0418	Life-long	Sullivan et al., 2011 ¹⁴¹
Non-traumatic fracture	-0.068	Transient	Sullivan et al., 2016 ¹⁴³
Psychiatric Events			
Anxiety, depression, mania, hyperactivity, psychosis, or delirium	-0.0896	Transient	Sullivan et al., 2011 ¹⁴¹
Gastrointestinal Events			
GI perforation	-0.0684	Transient	Sullivan et al., 2011 ¹⁴¹
Ulcer/GI bleed	-0.0569	Transient	Sullivan et al., 2011 ¹⁴¹

Gastritis	-0.0439	Transient	Sullivan et al., 2011 ¹⁴¹
Infection events			
Opportunistic infections	-0.1005	Transient	Matthews et al., 2019 ¹⁴⁷ , Malene et al., 2023 ¹⁴⁸
Sepsis	-0.2	Transient	Shah et al., 2022 ¹⁴⁹
Severe infection: hospitalizations	-0.156	Transient	TA480 (original source: Oppong et al., 2013) ¹⁵⁰
Ocular Events			
Cataract	-0.0334	Transient	Sullivan et al., 2011 ¹⁴¹
Glaucoma	-0.0385	Life-long	Sullivan et al., 2011 ¹⁴¹
Increased IOP	0	Transient	Assumption
Sleep Disorders			
Sleep disorders	-0.0372	Transient	Sullivan et al., 2011 ¹⁴¹
Dyspnea	-0.05	Transient	Doyle et al., 2008 ¹⁵¹
Skin Events			
Bruising	-0.0033	Transient	TA236 ¹⁵²
Skin thinning	-0.0033	Transient	Assumed same as bruising/skin thinning
Impaired wound healing	-0.0033	Transient	Assumed same as bruising/skin thinning
Acne	-0.0654	Transient	Sullivan et al., 2016 ¹⁴³
Others			
Hirsutism	-0.04495	Transient	Nafees et al., 2008 ¹⁵³

Abbreviations: AE, adverse event; BMI, body mass index; IOP, intraocular pressure; GI, gastrointestinal

3.4.4.3 Disutility related to JAKi-related AEs

Patients in the upadacitinib + 26-week corticosteroid tapering arm were at risk to develop JAKi-related AEs whilst actively receiving upadacitinib in the model.

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Corresponding utility decrements were applied. Estimates of the disutility due to JAKi-related AEs were obtained from literature and validated as the most patient relevant JAKi associated events by clinicians during the advisory board (Table 39).

Table 39. Disutilities of JAKi-related AEs

Adverse Events	Disutility	Duration	Source
MACE	-0.050	Transient	TA599 ¹⁵⁴
VTE	-0.111	Transient	TA607 ¹⁵⁵

Abbreviations: AE, adverse event; JAKi, Janus kinase inhibitors; MACE, major adverse cardiovascular events; VTE, venous thromboembolism

3.5 Cost and healthcare resource use identification, measurement and valuation

In line with NICE requirements, an SLR was conducted to identify studies reporting healthcare resource utilisation (HCRU) associated with the management of GCA. A full description of SLR methodology and outcomes is provided in Appendix G. Literature searches were designed applying a combined approach to identify evidence relating to economic evaluations, costs and healthcare resource utilisation, and health state utility studies; details of the searches are described previously in sections 3.1 and 3.4.1. PRISMA diagram for the original SLR and updated searches are presented in Figure 10 and Figure 15, respectively.

Of the studies eligible for inclusion in the combined SLR, 26 reported cost and/or HCRU in GCA populations. Most studies reported HCRU/costs from a European setting (n=13) or from the US and Canada (n=12). Almost all studies were retrospective (n=24), with four reporting the costs associated with GCA diagnosis, three the costs and burden associated with corticosteroid related AEs and the remainder relating to the broader management of GCA. Of studies reporting the cost burden of GCA, all focused on direct costs. The most common direct costs reported across studies were for overall hospitalisation, inpatient visits and pharmacy expenditure.

3.5.1 Intervention and comparators' costs and resource use

3.5.1.1 Drug acquisition cost

Drug acquisition costs applied in the CEA were calculated as a function of the unit drug costs and the dosing schedules for included treatments (Table 40). Dosing schedules were based on the SELECT-GCA trial protocol for upadacitinib and corticosteroid-tapering alone regimens.²² The cost of conventional corticosteroid treatment was estimated using published prices for prednisolone, as this is the most widely used CS for GCA.

Unit drug costs for upadacitinib were retrieved from the British National Formulary (BNF), and an average cost per mg was derived from generic prednisolone costs available via eMIT (Table 41).

In addition, the model incorporated a simple PAS discount – set at [REDACTED] in the base-case – to reflect the net price of upadacitinib. As a result, the final cost for each treatment cycle was calculated by applying the PAS discount to the unit drug cost, and then multiplying by the dosing schedule as specified in the model. This approach ensures that cost estimates accurately represent both the standard pricing and the savings conferred.

Table 40. Drug dosing schedules

Treatment arm	Drug component	Description of dosing schedule
UPA + 26 WK CS-T ²¹	Upadacitinib	15 mg daily (oral)
	Prednisolone	26 weeks as per tapering schedule (oral) (Section 3.3.5)
PBO+52 WK CS-T ²¹	Prednisolone	52 weeks as per tapering schedule (oral) (Section 3.3.5)

Abbreviations: CS-T, corticosteroid tapering; mg, milligram; PBO, placebo; UPA, upadacitinib, WK, week

Table 41. Unit drug costs

Treatment	Unit drug costs (GBP 2024/2025)		
	Cost per unit before discount	Cost per unit after discount	Cost per mg after discount
Upadacitinib	£28.77	[REDACTED]	[REDACTED]

Treatment	Unit drug costs (GBP 2024/2025)		
	Cost per unit before discount	Cost per unit after discount	Cost per mg after discount
Prednisolone	-	-	£0.05

Abbreviations: GBP, Great British Pound; mg, milligrams

3.5.1.2 Monitoring costs

Monitoring requirements during the treatment of upadacitinib were based on the expected UK licence, inferred from usage requirements in other licensed indications (Table 42).^{91,156} Monitoring services included blood tests, liver function tests, and lipid panel tests. Unit cost for each test were obtained from the NHS Reference Costs 2023/24 (Table 43).

Table 42. Weekly frequency of treatment monitoring during the treatment period

Test	Weekly frequency of monitoring services
	Upadacitinib
Full blood count	0.083
Liver function test	0.083
Lipid panel	0.083

Table 43. Unit costs of monitoring services

Service	Unit cost per service (2023/24 GBP)	Source
Full blood count	£2.98	NHS Reference Costs 2023/24
Liver function test	£1.53	
Lipid panel	£1.53	

Abbreviations: GBP, Great British Pound; NHS, National Health Service

3.5.2 Health-state unit costs and resource use

3.5.2.1 Disease management costs

The model estimated disease management weekly costs by considering the proportion of patients requiring a specialist visit and the average resource use cost for each health state.

- Remission state
 - Pre-flare remission on steroid
 - Pre-flare remission off steroid
 - Post-flare remission on steroid
 - Post-flare remission off steroid
- Flare state

The specialist management services included in disease management were rheumatologist, general practitioner (GP) service, geriatrician, ophthalmologist, neurologist, and other relevant specialties. Unit costs of specialist services were sourced from NHS reference costs 2023/24.

The disease management costs per week were derived based on weighted costs per service and weighted weekly resource use for each health state. The proportion of patients receiving each service and the distribution of visit frequencies for each health state were sourced from a market research study (Research Partnerships 2017), as applied and considered appropriate in TA518.²⁷ While data were available for pre-flare remission on- and off-steroids, post-flare remission on- and off-steroid subgroups were not separately reported and were reported for post-flare on-steroid only. Therefore, an assumption was made that the ratio of patients on versus off steroids in the post-flare remission state mirrored that observed in the pre-flare remission state. Specifically, the ratio was applied to the post-flare (on-steroid) remission proportions to derive corresponding proportions for the post-flare off-steroid subgroup.

The unit costs and proportion of patients receiving each service in the remission state, the distribution of visit frequencies, and corresponding weekly disease management costs in the remission state are summarised in Table 44 and Table 45.

The unit costs and proportion of patients receiving each service in flare state, the visit frequencies, and corresponding weekly disease management costs in flare state are summarised in Table 46 and Table 47.

Table 44. Unit service costs and proportion of patients receiving services in remission state

Procedures and monitoring services	Unit cost ([2023/24 GBP)	Proportion of patients receiving services – Remission
Rheumatologist	£181.45	65.35%
GP	£49.00	16.83%
Geriatrician	£367.45	9.90%
Ophthalmologist	£125.92	4.95%
Neurologist	£234.91	1.98%
Other	£170.48	0.99%
Weighted cost per service		£175.77

Abbreviations: GBP, Great British Pound; GP, general practitioner

Table 45. Distribution of visit frequency and disease management cost per week in remission state

Weekly resource use	Distribution of visit frequency			
	Pre-flare remission on-steroid	Pre-flare remission off-steroid	Post-flare remission on-steroid	Post-flare remission off-steroid
Weekly	4.60%	0.00%	1.90%	0.00%
Every 2 weeks	14.5 %	0.00%	9.40%	0.00%
Monthly	25.90%	1.10%	24.50%	1.04%
Every 2 months	12.7%	8.40%	13.20%	8.73%
Every 3 months	21.00%	16.80%	25.90%	20.72%
Every 6 months	13.00%	26.30%	16.50%	33.38%

Weekly resource use	Distribution of visit frequency			
	Pre-flare remission on-steroid	Pre-flare remission off-steroid	Post-flare remission on-steroid	Post-flare remission off-steroid
Weighted weekly resource use	0.22	0.04	0.17	0.04
Weekly disease management costs (2023/24 GBP)	£39.03	£6.72	£30.27	£7.86

Abbreviations: GBP, Great British Pound

Table 46. Unit service costs and proportion of patients receiving services in flare state

Procedures and monitoring services	Unit cost (2023/24 GBP)	Proportion of patients receiving services	
		Flare (first visit)	Flare (follow-up visit)
Rheumatologist	£181.45	24.75%	67.00%
GP	£49.00	58.42%	44.00%
Geriatrician	£367.45	1.98%	13.00%
Ophthalmologist	£125.92	6.93%	10.00%
Neurologist	£234.91	0.99%	6.00%
Other	£170.48	6.93%	5.00%
Weighted cost per service		£103.68	£226.11

Abbreviations: GBP, Great British Pound; GP, general practitioner

Table 47. Distribution of visit frequency and disease management cost per week in flare state

	Total	First visit	Follow-up visit
Mean number of visits per a flare event (4 weeks)	2.71	1	1.71
Weekly resource use	--	0.25	0.43
Weekly disease management costs (2023/24 GBP)	£122.58		

Abbreviations: GBP, Great British Pound

3.5.2.2 GCA complication costs

The GCA specific complications applied in the model are detailed in Section 3.3.2.3. For vision loss complications (both bilateral and unilateral), the model calculated a lifetime cost based on the patient's expected remaining discounted life years. This was calculated by adding the first-year unit cost to the product of the subsequent-year unit cost and the number of remaining discounted life years beyond the first year (based on the upadacitinib arm). In other words, the model applies:

$$\text{Lifetime cost} = \text{first year cost} + (\text{subsequent year cost} \times [\text{discounted LYs} - 1])$$

This ensures that the cost reflects how the lifetime cost for vision loss varied depending on the projected discounted life years; thus, capturing differences in patient longevity and ensuring that the cost reflects the true long-term burden of vision loss complications.

For patients with a non-fatal stroke (major or minor), a 5-year cost after the event was applied; and for patients who suffered aortic aneurysm, aortic dissection, or myocardial infarction, per event cost were applied. Costs associated with GCA complications were based on NHS Reference Costs 2023/24 and published literature (Table 48).

Table 48. Costs associated with GCA complications

GCA-related complications	Unit cost (2023/24 GBP)	Unit of cost	Reference
Vision loss (bilateral)	64,983.64	Lifetime	Luqmani et al. 2016 ¹⁵⁷
Vision loss (unilateral)	7,296.50	Lifetime	Alva et al. 2014 ¹⁵⁸
Aortic aneurysm	12,687.55	Per event	NHS Reference 2023/24 ¹⁵⁹
Aortic dissection	27,641.65	Per event	
Myocardial infarction	2,206.16	Per event	
Minor stroke	10,848.23	5-year cost	
Major stroke	25,318.74	5-year cost	

Abbreviations: GBP, Great British Pound

3.5.3 Adverse reaction unit costs and resource use

corticosteroid-related AEs and JAKi-related AEs are detailed in Section 3.3.2.2. Costs per AE episode were estimated based on NHS Reference Costs 2023/24 and published literature (Table 49 and Table 50). Consistent with the approach used for disutilities, corticosteroid-related AEs were categorised as either transient or lifelong, with costs applied accordingly. For transient AEs, a one-time per-event cost was applied in the cycle in which the AE occurred. For lifelong AEs, a recurring cost was applied on an ongoing basis in all subsequent cycles following onset. These ongoing costs were calculated as an annual cost divided by the number of weeks per year, then applied as a weekly cost to all patients who experience a given AE. In the absence of specific AE data, the cost of osteoporosis was estimated using the costs associated with commonly prescribed treatments for patients with osteoporosis.

Table 49. CS-related AE costs

CS-related AEs	Cost unit	AE costs (2023/24 GBP)	Sources
Metabolic Events			
Increased BMI	Per event	£0.00	Assumption
Pre-diabetes	Per event	£60.76	TA875 ¹⁶⁰
Type 2 diabetes	Per event	£1,679.56	TA875 ¹⁶⁰
Hyperlipidemia	Per year	£17.99	Mihaylova et al., 2022 ¹⁶¹
Endocrine adrenal insufficiency	Per event	£2,397.76	Chauhan et al., 2013 ¹⁶²
Cushing's syndrome	Per event	£1,099.22	NHS Reference 2023/24 ¹⁵⁹
Cardiovascular Events			
Hypertension	Per event	£758.83	NHS Reference 2023/24 ¹⁵⁹
Electrolytes (sodium, potassium) abnormalities	Per event	£1,764.35	NHS Reference 2023/24 ¹⁵⁹
Heart failure	Per year	£2,772.36	NHS Reference 2023/24 ¹⁵⁹

CS-related AEs	Cost unit	AE costs (2023/24 GBP)	Sources
Atherosclerosis	Per year	£1,157.01	NHS Reference 2023/24 ¹⁵⁹
Palpitations	Per event	£1,333.98	NHS Reference 2023/24 ¹⁵⁹
Musculoskeletal Events			
Myopathy	Per event	£1,004.02	NHS Reference 2023/24 ¹⁵⁹
Aseptic necrosis of bone	Per year	£2,335.47	NHS Reference 2023/24 ¹⁵⁹
Tendon rupture	Per year	£1,341.55	NHS Reference 2023/24 ¹⁵⁹
Bone Density Events			
Osteoporosis	Per year	£75.94	MIMS 2024 ¹⁶³ and Lewiecki et al., 2010 ¹⁶⁴
Non-traumatic fracture	Per event	£1,769.22	NHS Reference 2023/24 ¹⁵⁹
Gastrointestinal Events			
GI perforation	Per event	£6,195.24	NHS Reference 2023/24 ¹⁵⁹
Ulcer/GI bleed	Per event	£1,894.04	NHS Reference 2023/24 ¹⁵⁹
Gastritis	Per event	£1,903.83	NHS Reference 2023/24 ¹⁵⁹
Psychiatric Events			
Anxiety, depression, mania, hyperactivity, psychosis, or delirium	Per event	£2,869.29	NHS Reference 2023/24 ¹⁵⁹
Infection events			
Opportunistic infections	Per event	£2,282.03	NHS Reference 2023/24 ¹⁵⁹
Sepsis	Per event	£3,376.66	NHS Reference 2023/24 ¹⁵⁹
Severe infection: hospitalizations	Per event	£4,262.54	NHS Reference 2023/24 ¹⁵⁹
Ocular Events			

CS-related AEs	Cost unit	AE costs (2023/24 GBP)	Sources
Cataract	Per event	£1,266.97	NHS Reference 2023/24 ¹⁵⁹
Glaucoma	Per year	£827.32	NHS Reference 2023/24 ¹⁵⁹
Increased IOP	Per event	£0.00	Assumption
Sleep Disorders			
Sleep disorders	Per event	£969.73	NHS Reference 2023/24 ¹⁵⁹
Dyspnea	Per event	£1,666.53	NHS Reference 2023/24 ¹⁵⁹
Skin Events			
Bruising	Per event	£0.00	Assumption
Skin thinning	Per event	£0.00	Assumption
Impaired wound healing	Per event	£0.00	Assumption
Acne	Per event	£0.00	Assumption
Other			
Hirsutism	Per event	£0.00	Assumption

Abbreviations: AE, adverse event; BMI, body mass index; GBP, Great British Pound; IOP, intraocular pressure; GI, gastrointestinal; NHS, National Health Service

Table 50. JAKi-related AE costs

JAKi-related AEs	Cost unit	AE costs (2023/24 GBP)	Sources
MACE	Per event	£5,871.32	Kent et al. (2013) ¹⁶⁵
VTE	Per event	£1,739.38	NHS Reference 2023/24 ¹⁵⁹

Abbreviations: AE, adverse event; JAKi, Janus kinase inhibitors; MACE, major adverse cardiovascular events; VTE, venous thromboembolism

3.5.4 Miscellaneous unit costs and resource use

No additional healthcare resource use was included in the CEA.

3.6 Severity

Absolute and proportional QALY shortfall analyses were conducted reflecting SoC with corticosteroid-tapering. The thresholds for severity modifier were not reached so are not considered relevant to this appraisal.

3.7 Uncertainty

The inherent uncertainty in the CEA stems primarily from requiring short-term (52-week) trial data to predict long-term outcomes for a relapsing–remitting condition like GCA. As a result, key endpoints—such as TTFF and subsequent flares—required extrapolation beyond the observed trial period. To address this uncertainty, extensive clinical input and validation were sought to refine the extrapolation methods and align model fit to expected longer term trends in clinical practice, rather than relying solely on statistical goodness of fit; model predictions of cumulative flare over time were also validated against the published literature and shown to provide realistic estimations over a 5- and 10-year period (Section 3.3.1.2). Furthermore, scenario analyses have been conducted that explore alternative assumptions for both the extrapolation of flare rates, treatment duration, and varying hazard profiles (such as applying declining flare rates over time) which reflect the potential higher cumulative corticosteroid burden in SoC management. By integrating validation against the published literature and by clinical experts, with rigorous statistical methods and sensitivity analyses, the approach provides a robust and realistic projection of long-term outcomes, while aiming to transparently account for the uncertainty inherent to extrapolating short-term data.

Additionally, while the base-case analysis utilised the corticosteroid tapering schedule as observed in SELECT-GCA (following the approach to align with clinical trial data in TA518), clinical experts have indicated that longer-term tapering regimens are sometimes necessary in practice. This discrepancy suggests that the true cumulative corticosteroid burden associated with SoC could be underrepresented in the model.

3.8 Managed access proposal

The company is not intending to submit a managed access proposal. It is considered unlikely that additional data collection through the managed access scheme would provide evidence to address the key uncertainties within the submission.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

The base case inputs applied in the model are summarised in Table 51.

Table 51. Summary of variables applied in the economic model

Variables	Base case input	Reference to section in submission
Model setting		
Starting age (year)	71.1 years	3.2.1
Proportion of female (%)	73.1%	
Weight (kg), mean	69.3	
Time horizon (year)	Lifetime	3.3.1
Annual discount rate - costs	3.5%	
Annual discount rate - effects	3.5%	
Distribution of initial corticosteroid dose - UPA + 26-WK CS-T	60 mg: 9.57% 50 mg: 9.09% 40 mg: 28.71% 30 mg: 22.97% 20 mg: 29.67%	3.3.2
Distribution of initial corticosteroid dose - PBO + 52-WK CS-T	60 mg: 5.36% 50 mg: 14.29% 40 mg: 27.68% 30 mg: 25.89% 20 mg: 26.79%	
Effectiveness (weekly probability)		
TTFF - UPA + 26-WK CS-T	Log-normal	3.3.1
TTFF - PBO + 52-WK CS-T	Log-normal	
Probability of subsequent flare - UPA + 26-WK CS-T	0.0069	3.3.1
Probability of subsequent flare - PBO + 52-WK CS-T	0.0113	

Variables	Base case input	Reference to section in submission
Mortality		
Relative risk of all cause death – long-term (GCA patients versus general population)	1.03	3.3.1
Relative risk of all cause death – short-term (GCA patients versus general population)	1.49	
Treatment duration		
UPA + 26-WK CS-T (weeks)	104	3.3.3
Utilities		
Utility – Remission	0.7685	3.4.2
Utility – Flare	0.7098	
Total treatment cost per week		
Total treatment cost per week - Upadacitinib	████	3.5.1
Drug cost per mg - Prednisolone	£0.05	
Health care resource utilization and associated costs		
Weekly disease management cost - Pre-flare remission on steroid	£39.03	3.5.2
Weekly disease management cost - Pre-flare remission off steroid	£6.72	
Weekly disease management cost - Post-flare remission on steroids	£30.27	
Weekly disease management cost - Post-flare remission off steroids	£7.86	
Weekly disease management cost - flare	£122.58	
GCA complication costs		
Unit cost - Vision loss (bilateral) (lifetime cost)	£64,558.26	
Unit cost - Vision loss (unilateral) (lifetime cost)	£7,256.08	
Unit cost - Aortic aneurysm (per event)	£12,687.55	
Unit cost - Aortic dissection (per event)	£27,641.65	
Unit cost - Myocardial infarction (per event)	£2,206.16	
Unit cost - Minor stroke (5-year cost)	£10,848.23	
Unit cost - Major stroke (5-year cost)	£25,318.74	

Variables	Base case input	Reference to section in submission
Risk of GCA complications (weekly probability)		
Probability - Vision loss (bilateral)	0.0003	3.3.2.3
Probability - Vision loss (unilateral)	0.0031	
Probability - Aortic aneurysm	0.0002	
Probability - Aortic dissection	0.0001	
Probability - Myocardial infarction	0.0007	
Probability - Minor stroke	0.0042	
Probability - Major stroke	0.0028	
Disutilities - Vision loss (bilateral)	-0.220	3.4.4
Disutilities - Vision loss (unilateral)	-0.040	
Disutilities - Aortic aneurysm	-0.054	
Disutilities - Aortic dissection	-0.129	
Disutilities – Myocardial infarction	-0.063	
Disutilities – Old myocardial infarction	-0.037	
Disutilities - Minor stroke	-0.033	
Disutilities - Major stroke	-0.101	
Costs - GCA complications	See Table 48	3.5.2.2
Safety		
Annual CS-related AE rates (low dose/medium dose/high dose/very high dose)	See Table 31	3.3.2.2
Disutility – CS-related AEs	See Table 38	3.4.4.2
Weekly JAKi-related AE rate - MACE	0.0001	3.3.2.4
Weekly JAKi-related AE rate - VTE	0.0001	
Disutility – MACE	-0.050	3.3.2.4
Disutility – VTE	-0.111	
Costs		
Costs - CS-related AEs	See Table 49	3.5.3
Costs - JAKi-related AEs – MACE	£5,871.32	
Costs – JAKi-related AEs - VTE	£1,739.38	

Abbreviations: AE, adverse event; CS-T, corticosteroid tapering; GCA, giant cell arteritis; JAKi, Janus kinase inhibitors; MACE, major adverse cardiovascular events; PBO, placebo; VTE, UPA, upadacitinib; venous thromboembolism; WK, week

3.9.2 Assumptions

During the development of the CEA, assumptions were required where there was uncertainty in published evidence or lack of accepted precedent to inform the model. Key model assumptions are detailed in Table 52.

Table 52. Assumptions in the CEA

Parameter	Assumptions	Justification
Time horizon	Lifetime	A lifetime horizon was used in order to sufficiently capture all relevant costs and benefits associated with the treatments. Other time horizons were tested in scenario analyses.
Effectiveness	After the initial flare, patients in each treatment arm were assumed to have a constant risk of subsequent flares, irrespective of their current GC dose. This implies that patients faced a continuous risk of flares throughout their lifetime, with the constant risk varying across treatment arms	Andersson et al. reported that relapses or flares can occur at any time after diagnosis, particularly when treatment withdrawal is attempted ¹⁶⁶ . According to BSR guidelines, most early relapses are attributed to rapid glucocorticoid tapering ¹⁶⁷ .
Corticosteroid related events	Corticosteroid related AE rates and cumulative corticosteroid thresholds are derived from an RWE study due to low event rates from the relatively short-term SELECT-GCA trial and the long-term nature of these events. ⁴⁴ Patients enrolled into the RWE study had predominantly new-onset GCA, but AE rates from the study are applied to the overall GCA population in the current analysis	It is likely that patients with relapsing GCA will have a higher cumulative corticosteroid dose at baseline than patients with new-onset disease in clinical practice. As a result, this assumption of considering RWE data generalisable to all GCA populations modelled is considered to be conservative, which may underestimate the true corticosteroid related AE burden for patients in the analysis, and subsequently the benefits of cumulative corticosteroid dose reduction resulting from upadacitinib treatment. In addition, the population and outcomes from the RWE study were validated by clinicians at the advisory board and considered to be reflective of the UK GCA population in practice with all AEs suitably linked to corticosteroid exposure.
Flare/GCA complications	Flares were assumed to last for a duration of 4 weeks, and no cap was placed upon the number of flares a patient could experience. GCA-related complications could only occur from the flare health state. Following flare patients were assumed to resume the previous dose on their tapering schedule	The BSR guidelines and Royal College of Physicians suggested that symptoms of a flare can continue for at least 4 weeks ¹⁶⁷ . According to the protocols of SELECT-GCA ²² and GiACTA ⁹¹ , a patient should resume a full week of their last effective dose before tapering following a flare.

Parameter	Assumptions	Justification
	unless they experience a severe flare.	Additionally, a scenario analysis was conducted to test a declining risk over time in response to clinician feedback.
Treatment duration	Upadacitinib treatment duration is assumed to be independent of patient response, with a fixed 2-year duration in the base-case analysis.	Although the SELECT-GCA trial used a 1-year treatment period, clinical experts and NICE scope consultees suggest that, in practice, patients may require longer treatment durations to avoid relapse and associated corticosteroid use. This extended duration better reflects real-world treatment needs and aligns with the 2-year corticosteroid tapering schedule recommended in clinical guidelines (BSR and EULAR). GCA is a chronic, heterogeneous disease; to align with clinician feedback that a proportion of patients will require extended treatment, with some needing treatment for the remainder of their lives, scenario analyses further explored longer durations up to lifetime. The aim of the analysis was to address the known unmet need in GCA, by providing flexible treatment durations guided by patient preference and clinician judgement in response to disease activity.
Utilities	Disutilities associated with flare, GCA complications, and common corticosteroid-related AEs were additive.	These disutilities reflected distinctly different health impacts, allowing their effects to be combined using this approach.
Mortality	All-cause mortality considered (adjusted using a relative risk), and the GCA-related mortality risk was assumed to be the same across all health states and would not differ between treatment arms.	Adjusted all-cause mortality is appropriate to consider in a lifetime model. Mortality was applied based on the age of the cohort in each cycle of the model, using a weighted average of female and male mortality rates. The starting age and gender distribution of the model cohort was based on the pooled ITT population from SELECT-GCA. There is no evidence of a treatment effect on life expectancy, however patients with GCA have shown a higher mortality rate than the general public. Therefore, the all-cause mortality was adjusted by applying a relative risk of 1.49 in the first year following flare (accounting for higher risk) and 1.03 thereafter. ¹⁰⁴

Parameter	Assumptions	Justification
Safety	Corticosteroid-related AEs included in the model were categorised into transient or life-long. Transient events were assumed to incur a fixed cost and disutility at the time of event occurrence, while life-long events were assumed to result in ongoing costs and disutility throughout the patient's lifetime.	Some of AEs are considered irreversible. This assumption fully accounts for their impact on the model outcomes.

Abbreviations: AE, adverse event; BSR, British Society for Rheumatology; GCA, giant cell arteritis; RWE: real-world evidence

3.10 Base-case results

3.10.1 Base-case incremental cost-effectiveness analysis results

The base-case analysis (Table 53) demonstrates that upadacitinib delivers substantial economic and clinical benefits compared to the standard 52-week corticosteroid tapering regimen. With the PAS applied, the total cost of upadacitinib is reduced, resulting in total costs of [REDACTED] and producing 10.634 LYs and [REDACTED] QALYs. In comparison, the standard corticosteroid regimen costs [REDACTED] and yields 10.581 LYs and [REDACTED] QALYs. This translates into incremental cost savings of roughly [REDACTED] per patient, alongside an average gain of 0.053 LYs and [REDACTED] QALYs. These outcomes indicate that upadacitinib is dominant, offering improved health outcomes at lower overall costs.

At a £20,000 threshold the incremental net monetary benefit (NMB) is [REDACTED] and the incremental net health benefit (NHB) is [REDACTED] QALYs (Table 54). At a £30,000 threshold, the NMB is [REDACTED] and the NHB is [REDACTED] QALYs (Table 54). Both metrics confirm that upadacitinib is dominant in the GCA population.

Table 53. Base-case results

	Total			Incremental			
Technologies	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	ICER (£/QALY)

UPA + 26-WK CS-T	████	10.634	████	████	0.053	████	Dominant
PBO + 52-WK CS-T	████	10.581	████	-	-	-	-

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; QALYs, quality-adjusted life years

Table 54. Net monetary and net health benefit

Net Monetary Benefit (NMB) at:		Net Health Benefit (NHB) at:	
£20,000	£30,000	£20,000	£30,000
████	████	████	████

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years

3.11 Exploring uncertainty

Deterministic and probabilistic sensitivity analyses were performed, which explored the robustness of the base-case cost-effectiveness estimates to the key model assumptions and model parameters. Additionally, scenario analyses were conducted to assess uncertainties. These included varying treatment duration, changing the application of treatment waning, varying the rate of subsequent flares, and varying selected AEs to match the AEs used in TA518. This ensures the model reflects plausible variation in clinical practice and long-term disease progression.

3.11.1 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the model sampled values from probability distributions around the mean of each input, using the standard error (SE) to estimate plausible values based on the appropriate distribution. This approach allowed for simultaneously variation of all model parameters across 1,000 iterations, aligning with NICE guidance, that recommends selecting a sufficient number of iterations to ensure convergence towards stable, stochastic results.¹⁶⁸

The distribution used for each parameter in the PSA (and DSA) followed the recommendations of Briggs et al. (2006).¹⁶⁹ Correlated parameters, such as proportions or shares, were modelled through a Dirichlet distribution where applicable. Table 55 lists the parameters and their corresponding distributions. Where possible, the parameters of these distributions were informed by deterministic values and their associated SEs. In cases where SEs are unavailable, a default SE of 20% was applied, consistent with assumptions used in prior NICE submissions.¹⁷⁰

The findings are presented by means of the CEAC, cost-effectiveness acceptability frontier (CEAF), and a scatter plot of the incremental cost versus the incremental QALYs. Mean total costs, mean total QALYs, and the mean probabilistic ICER are presented versus corticosteroids.

Table 55. PSA inputs

Parameter	PSA distribution	Base-case mean	SE	Comment
Baseline characteristics				
Starting age (year)	Normal	71.10	0.38	--
Proportion of female	Beta	0.7310	0.1462	--
Weight (kg), mean	Normal	69.27	0.77	--
Effectiveness				
Parameters of the selected extrapolation models for TTFF	Multivariate normal	Shown in Figure 12 and Figure 13	NA	PSA inputs based on Cholesky decomposition matrix
Probability of Subsequent Flare - Upadacitinib	Beta	Shown in Table 51	--	SE assumed to be equal to 20% of the base-case value
Probability of Subsequent Flare – corticosteroid comparator	Beta	Shown in Table 51	--	
Treatment costs				
Drug cost and monitoring cost	Gamma	Shown in Table 41 and Table 43	--	SE assumed to be equal to 20% of the base-case value
Utility				
Remission	Beta	Shown in Table 51	0.010 / 0.015	Based on trial data
Disutility of flare	Beta	Shown in Table 51	0.030 / 0.048	Based on trial data
HCRU				
Disease management cost	Gamma	Shown in Table 45 and Table 47	--	SE assumed to be equal to 20% of the base-case value
Probability of GCA complications	Beta	Shown in Table 32	--	SE assumed to be equal to 20% of the base-case value

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Parameter	PSA distribution	Base-case mean	SE	Comment
GCA complication costs	Gamma	Shown in Table 48	--	SE assumed to be equal to 20% of the base-case value
Disutility due to GCA complications	Beta	Shown in Table 37	--	SE assumed to be equal to 20% of the base-case value
Safety				
CS-related AE rates	Beta	Shown in Table 31	--	SE assumed to be equal to 20% of the base-case value
JAKi-related AE rates	Beta	Shown in Table 33	--	SE assumed to be equal to 20% of the base-case value
Disutility due to CS-related AEs	Beta	Shown in Table 38	--	SE assumed to be equal to 20% of the base-case value
Disutility due to JAKi-related AEs	Beta	Shown in Table 39	--	SE assumed to be equal to 20% of the base-case value
CS-related AE costs	Gamma	Shown in Table 49	--	SE assumed to be equal to 20% of the base-case value
JAKi-related AE costs	Gamma	Shown in Table 50	--	SE assumed to be equal to 20% of the base-case value
Life table				
Relative risk of all cause death (short-term)	Lognormal	1.49	0.0475	Based on CI from Therkildsen 2022
Relative risk of all cause death (long-term)	Lognormal	1.03	0.0125	Based on CI from Therkildsen 2022

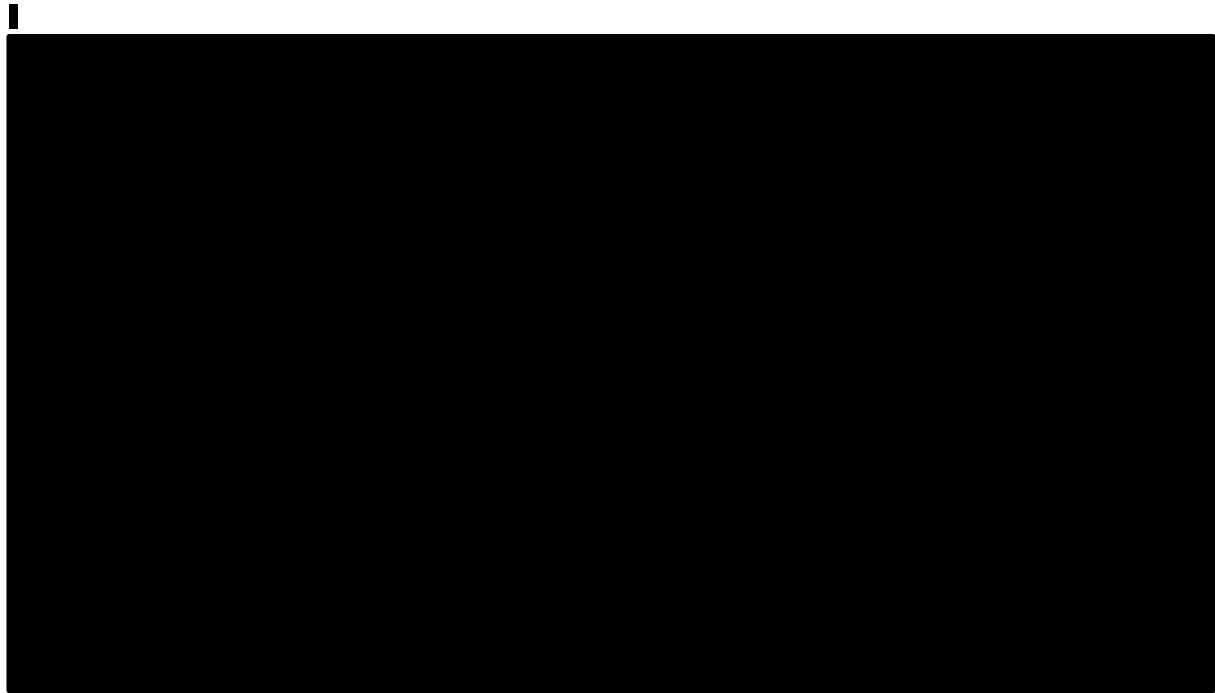
Abbreviations: AE: adverse event; CS: corticosteroids; GCA: Giant cell arteritis; HCRU: healthcare resource utilization; JAKi: Janus kinase inhibitors; PBO: placebo; PSA: probabilistic sensitivity analysis; SE: standard error; TTF: time to first flare

Company evidence submission template for upadacitinib for giant cell arteritis [ID6299]

3.11.2 Probabilistic sensitivity analysis results

The cost-effectiveness scatter plot and cost-effectiveness acceptability curves for upadacitinib compared with corticosteroids, arising from 1,000 simulations of the model with all parameters sampled, are presented in Figure 16 and Figure 17.

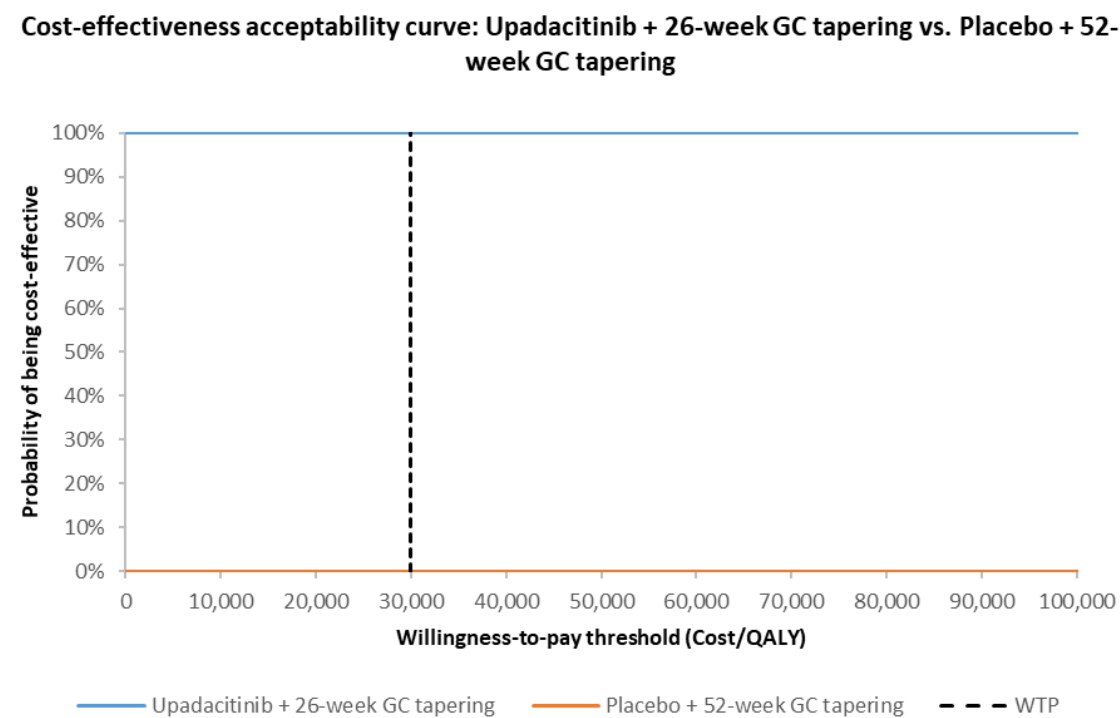
Figure 16. Cost-effectiveness scatter plot for upadacitinib versus CS



Analysis performed at upadacitinib PAS price

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; WTP, willingness-to-pay

Figure 17. Cost-effectiveness acceptability curve for upadacitinib versus CS



Analysis performed at upadacitinib PAS price
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; WTP, willingness-to-pay

Based on these analyses, the probability that upadacitinib is cost-effective versus corticosteroid is 100% at any WTP threshold.

The results of the PSA using the base case settings are presented in Table 56. The results further reinforce the robustness of the deterministic base-case findings. When accounting for parameter uncertainty, upadacitinib with a two-year treatment duration consistently dominated the comparator (52-week corticosteroid tapering). On average, upadacitinib delivered [REDACTED] additional QALYs and 0.053 additional LYs, while reducing total costs by [REDACTED] per patient. These findings confirm that, even when variability in key inputs is taken into account, upadacitinib remains a dominant strategy—providing better health outcomes at a lower overall cost compared to SoC.

Table 56. Probabilistic base-case results (with PAS) – overall population

Technologies	Total			Incremental			
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	ICER (£/QALY)
UPA + 26-WK CS-T		10.646			0.053		Dominant
PBO + 52-WK CS-T		10.593		-	-	-	-

Note: Costs and QALYs discounted; LYs undiscounted
ICER, incremental cost-effectiveness ratio; LY: life years; QALYs, quality-adjusted life years

3.11.3 Deterministic sensitivity analysis

Main drivers of model outcomes were analysed by means of a DSA. The distribution chosen for each parameter included in the DSA (and PSA) was based on the recommendations provided in Briggs et al. (2006).¹⁶⁹ Where available, lower and upper bounds for the DSA were determined by the SE or confidence intervals (CIs) from input estimates. In absence of estimates of variance, an SE level of 20% was assumed in line with prior NICE appraisals.¹⁷⁰ The DSA results and details on parameters varied are displayed in Figure 18 and Appendix K. Results demonstrated a high level of robustness. Across all tested parameters upadacitinib remained dominant compared with corticosteroid alone. Key model drivers included the weekly cost of upadacitinib, annual discount rate of costs, and flare probabilities. When adjusted to their upper and lower bounds, the ICER remained below zero, indicating cost savings alongside improved outcomes.

Figure 18. DSA tornado plot for upadacitinib versus CS



*Analysis performed using upadacitinib PAS price.

3.11.4 Scenario analysis

Details and cost-effectiveness outcomes of scenario analyses are summarised in Table 57. Across nearly all scenarios, upadacitinib remained dominant, indicating that it consistently delivered greater health benefits at a lower cost compared to corticosteroids alone.

Table 57. Scenario analyses

Base-case assumption	Scenario	Inc. costs	Inc. LYs	Inc. QALYs	Inc. ICER (£/QALY)
Base-case		████	0.053	████	Dominant
Patients experience severe flares restart corticosteroid at 40mg	Severe flare rate 0% - no severe flares	████	0.053	████	Dominant
	Restart at 60mg	████	0.053	████	Dominant
Constant subsequent flare rate for both arms	Declining subsequent flare rate over time (annual reduction of 5%)	████	0.045	████	Dominant
	Declining subsequent flare rate over time (annual reduction of 10%)	████	0.038	████	Dominant
2-year treatment duration for upadacitinib	3-year treatment duration	████	0.071	████	Dominant
	5-year treatment duration	████	0.101	████	Dominant
	10-year treatment duration	████	0.161	████	£7,988
	Lifetime treatment duration	████	0.244	████	£16,826
Immediate treatment waning post-treatment to placebo	No treatment waning effect post treatment discontinuation	████	0.244	████	Dominant
	Treatment waning period of 1 year	████	0.062	████	Dominant
SELECT-GCA utility values	GiACTA utility values	████	0.053	████	Dominant
Lifetime horizon	10-year time horizon	████	0.026	████	Dominant
	15-year time horizon	████	0.040	████	Dominant

Base-case assumption	Scenario	Inc. costs	Inc. LYs	Inc. QALYs	Inc. ICER (£/QALY)
CS-related AEs	Only include CS- related AEs included in TA518	■	0.053	■	£2,705

Abbreviations: Inc, incremental; LY, life year; ICER: incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Adjusting assumptions related to severe flares, such as assuming no severe flares or restarting corticosteroid at 60mg, resulted in only modest changes in QALYs and costs. Similarly, modelling a declining subsequent flare rate over time slightly reduced the incremental QALY gain (■ with 10% decline vs. ■ in the base case) and incremental cost savings, but the treatment remained dominant, reinforcing CEA resilience to alternative flare assumptions.

Scenarios exploring extended treatment durations for upadacitinib had the greatest impact on the cost-effectiveness results but consistently demonstrated that the treatment remains a cost-effective option up to a lifetime treatment duration. At 3-year and 5-year durations, upadacitinib continued to deliver both greater QALY gains and cost savings versus corticosteroid alone. When treatment duration was further extended to 10 years or lifetime, upadacitinib remained well within accepted cost-effectiveness thresholds, with ICERs of £7,988 and £16,826 per QALY, respectively. Scenarios demonstrate that upadacitinib can support sustained disease control and remain cost-effective, independent of treatment duration. This offers the potential for it to be a treatment option with flexible duration, guided by clinicians' judgement and the patients' disease activity.

Removing the assumption of treatment waning once patients discontinue treatment strengthened upadacitinib's cost-effectiveness profile. Whilst applying a 1-year waning period yielded reduced cost savings, it also led to greater QALY gains compared to the base-case, with upadacitinib remaining dominant. Using health state utilities derived from GiACTA in place of SELECT-GCA values had minimal impact on outcomes.

When restricted to shorter time horizons, the cost-effectiveness of upadacitinib was predictably reduced, as the full benefits of treatment had less time to accumulate.

Nevertheless, at a 10-year and 15-year time horizon, the treatment remained dominant. This shift reflects the fact that key benefits of upadacitinib (such as reduced flares, steroid tapering resulting in a reduction of cumulative corticosteroid exposure, and prevention of associated GCA complications and corticosteroid-related AEs) are fully realised over longer timeframes. This highlights a key limitation of applying a truncated time horizon in a chronic, relapsing-remitting condition like GCA, where the natural history of the disease and the consequences of cumulative corticosteroid use unfold over many years. A short-term horizon does not capture the full burden of flares or the progressive accrual of corticosteroid-related AEs and may underestimate the true extent of health benefits and cost savings associated with an effective treatment that reduces reliance on steroids. For this reason, the lifetime horizon adopted in the base case analysis was considered the most appropriate to model a chronic disease like GCA and for capturing the value of upadacitinib to all GCA patients.

Finally, limiting the analysis to only the corticosteroid-related AEs included in TA518 (i.e., fractures, diabetes, osteoporosis and infections) increases the ICER to £2,075 per QALY. Despite the limited corticosteroid-related AEs included in the scenario, upadacitinib remains cost-effective, proving the robustness of the results. However, these results are likely an underestimation of the value of a steroid sparing therapy.

3.12 Benefits not captured in the QALY calculation

GCA impacts all aspects of day-to-day life – employment, family life, finance, fatigue, and sleep disruption – all of which would benefit from a well-tolerated, effective, long-term therapy. Treating patients with upadacitinib decreases their risk of flare, sustains remission and reduces exposure to corticosteroid and all the detrimental health effects that come with it. Whilst the CEA aimed to capture the impacts of cumulative steroid burden and associated AEs, the full long-term effects and mortality risk associated with each event may be underestimated in the model.

Caring for a family member with GCA is a considerable burden, due to the disruptive impact that initial diagnosis and disease management may have on daily routine and the emotional distress of serious GCA associated risks. Treatment that sustains GCA remission and reduces risk of flare may in turn reduce patients' anxiety around disease relapse and improve the mental health of their carers. The impact upon care givers may be elevated in GCA specifically, as patients and their partners (primary caregivers) are predominantly elderly, with a peak GCA incidence between 70–79 years. Preventing disease relapse for patients will support carers in returning to normal life, both in their employment where patient's children are required to assist and caring for other family members. No data on family and caregivers' burden was obtained during SELECT-GCA, however, it is likely that patient and carer submissions will reflect this impact, as was recognised by the committee members during TA518.

Consideration should also be given to upadacitinib's route of administration, with patient preference for once daily oral tablets. In an elderly population, the short half-life of upadacitinib is also notable and potentially advantageous when there is a requirement to stop treatment quickly in the occurrence of opportunistic infections.

3.13 Validation

3.13.1 Validation of cost-effectiveness analysis

Following the Professional Society for Health Economics and Outcomes Research Good Research practice guidelines on model validation and transparency, the following aspects of model validation were assessed:

- Model verification – the major spreadsheet calculations and VBA subroutines were assessed for accuracy, and to ensure they operate as intended. Model parameters were reviewed against their source, to ensure that there are no transcription errors. Input derivation and implementation were reviewed, to ensure that the inputs were derived and implemented correctly. Sensitivity and extreme value analysis were conducted to ensure model output is internally

consistent and that the direction and magnitude of model outputs behave as expected.

- Model face validity – the model structure, key model assumptions and inputs have been validated by health economic and clinical experts specialising in the treatment of GCA.
- Model external validity – The model outcomes for the corticosteroid comparator arm were validated against outcomes reported in TA518, ensuring that model predictions were clinically valid.²⁷

3.14 Interpretation and conclusions of economic evidence

3.14.1 Summary of evidence

In the base case analysis, upadacitinib was associated with an incremental gain of ■■■ QALYs and a cost saving of ■■■ per patient compared with a 52-week corticosteroid tapering regimen, resulting in dominance. These findings were consistent across clinical subgroups (included in Appendix C). Across all analyses, upadacitinib was shown to deliver greater health benefits at a lower cost than corticosteroids alone.

Net benefit results further support this conclusion, with incremental NMB exceeding £25,000 at a WTP threshold of £20,000 per QALY, and NHB consistently showing QALY gains. The PSA confirmed the robustness of these findings, with upadacitinib dominating corticosteroids in all 1,000 simulations. DSA showed that results were stable across a wide range of parameter values, with upadacitinib remaining dominant in all cases.

Scenario analyses reinforced the strength of the economic case for upadacitinib. Cost-effectiveness was preserved across variations in flare assumptions, treatment duration, utility values, and the inclusion of certain corticosteroid related AE. Upadacitinib remained dominant or cost-effective even when treatment was modelled over extended durations (e.g. lifetime) or under more conservative assumptions.

While the cost-effectiveness of upadacitinib diminished when assessed over shorter time horizons, the treatment remained cost-effective at 10 and 15 years.

Taken together, these results demonstrate that upadacitinib provides a cost-effective use of NHS resources across the full GCA population. Given the consistent dominance observed in both new onset and relapsing subpopulations (Appendix C), the strong performance under uncertainty, and the sustained value across various scenarios, the economic evidence supports the conclusion that upadacitinib offers substantial clinical and economic benefit for all GCA patients. Furthermore, the model likely underestimates the full value of treatment, as it does not capture broader benefits such as improvements in quality of life from steroid reduction, increased convenience, or reductions in longer-term healthcare burden.

3.14.2 Relevance and generalisability

The economic evaluation is relevant to the UK setting, offering valuable insights to support decision-making related to the treatment of all adult patients with GCA. The population considered in the economic evaluation is considered most reflective of the expected license indication for upadacitinib and addressing the NICE scope. In line with TA518,²⁷ clinical efficacy was also explored for in new-onset and relapsing GCA subgroups and are presented in Appendix C, based on pre-defined subgroup analyses from SELECT-GCA.

Consultation with clinicians emphasised that patients with prior corticosteroid toxicity, patients who are unsuitable for tocilizumab, and those following tocilizumab completion will receive corticosteroids in clinical practice to control disease flare given the lack of alternative treatment options and risk of serious GCA related complications without treatment. As a result, the cost-effective analysis explored against corticosteroids captures these patients.

External clinical validation of economic model inputs and outcomes has been conducted to ensure TTFF extrapolations, predictions of cumulative steroid burden, the impact of specific corticosteroid-related AEs and subsequent flare rates over the

long-term duration are reflective of published literature and clinical experience in UK practice. In addition, efforts have been taken wherever possible to accurately reflect GCA patients and healthcare practice in the UK through alignment to committee preferred assumptions during TA518.

3.14.3 Strengths of the economic evaluation

From NICE scope consultees,⁴⁷ recent publications from TOC STOP,²⁸ and clinical expert feedback, it is evident there is a major unmet need for a flexible duration corticosteroid-sparing therapy for patients with GCA. This appraisal aims to address this need by demonstrating cost-effectiveness of upadacitinib across various treatment durations, reflecting variable potential individual treatment lengths determined by patient preferences and clinician judgement based on disease activity.

Where appropriate, CEA inputs were based on SELECT-GCA data, a high-quality phase 3 trial. Whilst no notable increase in JAKi associated events (VTE and MACE) were associated with upadacitinib in SELECT-GCA, in consideration of broader safety concerns with the JAKi drug class, the conservative approach to include these events in the analysis based on evidence from other indications was taken. Given the impact of corticosteroid exposure and related AEs, the CEA included a broad list of corticosteroid related AEs to capture their full burden to patients. With clinical experts highlighting that AE rates in SELECT-GCA trial are relatively low due to their long-term nature and may not fully represent the burden of corticosteroids, data from a longer-term RWE study were incorporated. The population and findings from the RWE study have been extensively validated with clinical experts and published literature to ensure outcomes are reflective of contemporary UK practice. In addition to ensuring key model assumptions were clinically validated, extensive scenario analyses have been conducted to explore uncertainty in the CEA.

3.14.4 Limitations of the economic evaluation

Limited evidence on corticosteroid related AEs was observed in SELECT-GCA given the long-term nature of these AEs and the relatively short-term follow up available. In line with the approach taken in TA518, and with consideration of the importance of

corticosteroid-burden to patients with GCA, corticosteroid related AEs were derived from a large RWE study with long-term follow-up.⁴⁴

Short-term data from SELECT-GCA necessitated flare rate (TTFF) extrapolations based on the observed 52-week data; the paucity of evidence and contemporary appraisals in GCA also resulted in assumptions being required on flare duration and corticosteroid tapering in clinical practice. Wherever possible, these assumptions have been validated with clinical experts and against the published literature to ensure they are an appropriate reflection of UK practice. Furthermore, scenario analyses have been conducted around each variable, showing the robustness of upadacitinib cost-effectiveness estimates to alternative assumptions.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Upadacitinib for treating giant cell arteritis [ID6299]

Addendum: Efficacy and Safety of Upadacitinib in Giant Cell Arteritis: 2-Year Interim-Results From the Re-Randomized, Double-Blind SELECT-GCA Phase 3 Trial

November 2025

File name	Version	Contains confidential information	Date
[ID6221] Upadacitinib Addendum [CON]	1.0	No	21 November 2025

SELECT-GCA Study Design

As described in the company submission (section 2.3.1), SELECT-GCA was a phase 3, randomised, double-blind, placebo-controlled, multicentre, multinational trial enrolling 429 adult subjects (≥ 50 years) with a diagnosis of active GCA, either new onset or relapsing disease, within 8 weeks of baseline. The study design is split into two periods, each with specific objectives and distinct patient populations.

- **Period 1:** To evaluate the efficacy and safety of upadacitinib 7.5 or 15 mg once daily with a 26-week corticosteroid (CS) taper regimen compared to placebo in combination with a 52-week CS taper regimen in subjects with new onset or relapsing GCA, as measured by the proportion of subjects in sustained remission at Week 52.
- **Period 2:** To evaluate the safety and efficacy of continuing versus withdrawing upadacitinib in maintaining remission in subjects who achieved remission in Period 1.

At the time of submission, only preliminary safety data were available for Period 2, and were included in the company submission. Since then, the interim efficacy and safety results for Period 2 of the SELECT-GCA trial have become available and described in this addendum to support the submission.

The study design is shown in Figure 1. Eligibility for entry into Period 2 required patients to be in remission at the end of Period 1, according to two pre-defined criteria:

- **R1 Population:** Patients who maintained remission for at least 24 consecutive weeks prior to Week 52.
- **R2 Population:** Patients who were in remission at Week 52 but had not met the 24-week sustained remission criterion. Patients who did not meet either R1 or R2 criteria were discontinued from the study at Week 52.

Eligible patients were re-randomised at a 2:1 ratio to either continue upadacitinib or switch to placebo. This addendum reports interim efficacy results on patients who met the R1 criteria and pooled safety results for patients who met the R1 and R2 criteria. Although the SELECT-GCA trial included two doses of upadacitinib, 7.5 and 15 mg,

the market authorisation is for a 15 mg dose in patients with GCA. Therefore, this addendum only contains relevant data for the upadacitinib 15 mg dose.

2-Year Topline Results

In the re-randomised study, continuous treatment with upadacitinib 15 mg in patients who had achieved sustained remission in Period 1 (R1 population) resulted in maintenance of remission at Week 104 in 67.3% of patients, compared to 28.6% for those switched to placebo (Figure 3). Those on continuous upadacitinib showed a 90% reduction in risk of experiencing a disease flare compared to those who switched to placebo during Period 2. Furthermore, in the patients who continued upadacitinib 15 mg treatment demonstrated a statistically significant reduction in median cumulative corticosteroid exposure compared to those who switched to the placebo arm (Figure 5, median: UPA/UPA: 0 mg versus UPA/PBO: 1048 mg; $p < 0.0001$ [nominal]). The data indicate continued treatment with upadacitinib 15 mg beyond 1-year results in sustained disease control, a significant reduction in cumulative steroid use, and a consistent safety profile with Period 1.

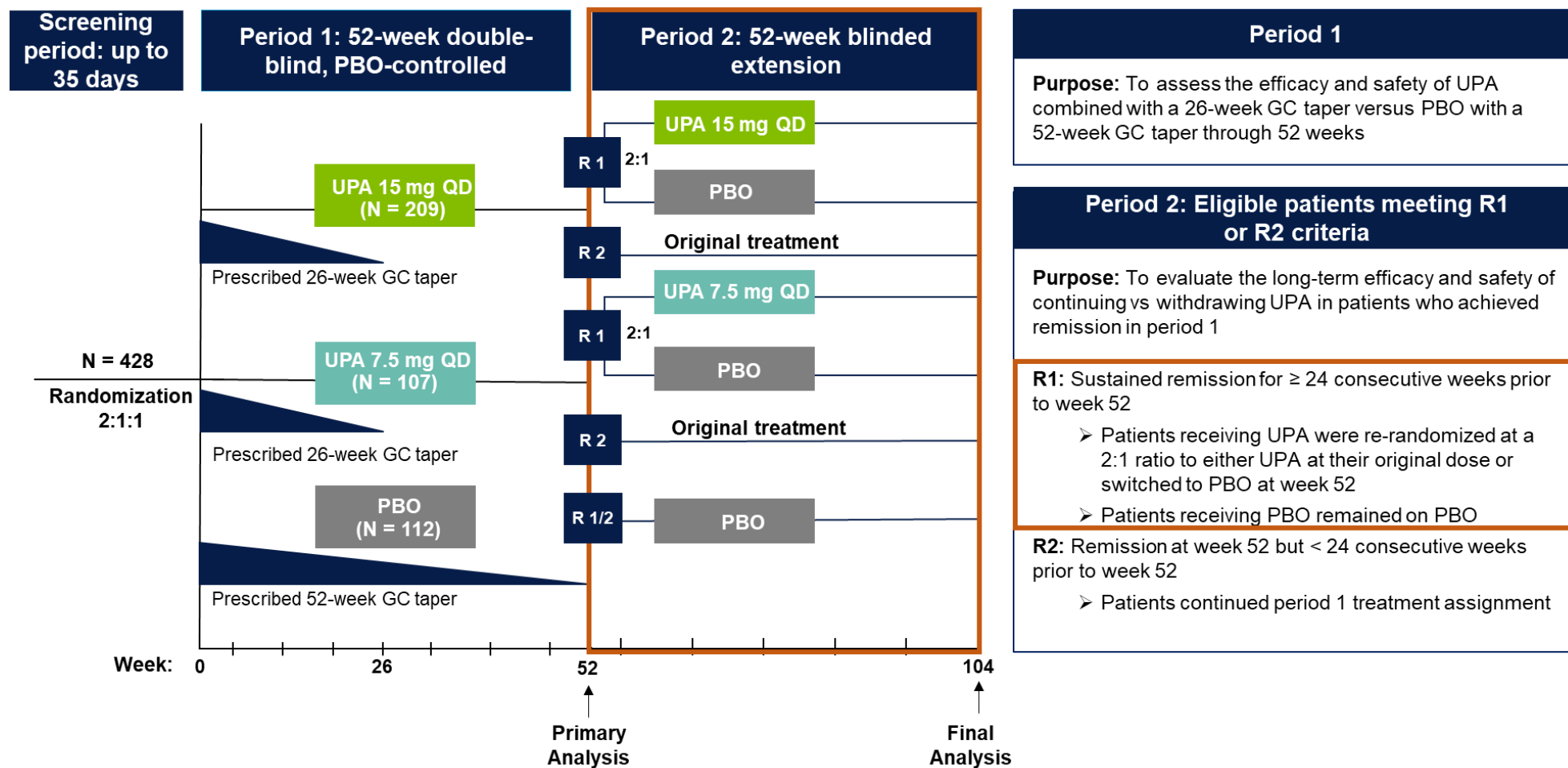


Figure 1. SELECT-GCA study design

Abbreviations: GC, glucocorticoid; PBO, placebo; QD, once daily; UPA, upadacitinib.

Definitions of flare and remission-based assessments in Period 2

The definitions of terms used to describe the course of GCA disease during Period 2 are shown in Table 1.

Table 1. Period 2 definitions of flare and remission-based assessments

Term	Definition
Disease flare	• Recurrence of signs or symptoms of GCA <i>or</i> ESR > 30 mm/hour (attributable to GCA) • Requiring reinitiation of GCs
Remission	• Absence of signs and symptoms of GCA • No GC use for GCA
Complete remission	• Remission • Normalization of ESR ($\leq$ 30 mm/hour)[†] • Normalization of hsCRP (< 1 mg/dL)
Cumulative dose of GCs	• Total amount of GCs, in mg of prednisone equivalent, received from Week 52 to Week 104

[†] If ESR > 30 mm/hour and the elevation was not attributable to GCA, this criterion could still be met.

Abbreviations: ESR, erythrocyte sedimentation rate; GC, glucocorticoid; GCA, giant cell arteritis; hsCRP, high-sensitivity C-reactive protein

Disposition and baseline characteristics of patients entering Period 2

One hundred and eighty-one subjects achieved remission for $\geq$ 24 consecutive weeks prior to Week 52 during Period 1 and thus met R1 criteria and entered Period 2. Of these, the majority (91%) completed the study, with 82% (149/181) remaining on study drug (Figure 2). No patients who remained on upadacitinib 7.5 mg or 15 mg in Period 2 discontinued due to lack of efficacy. Baseline characteristics for these patients are shown in Table 2.

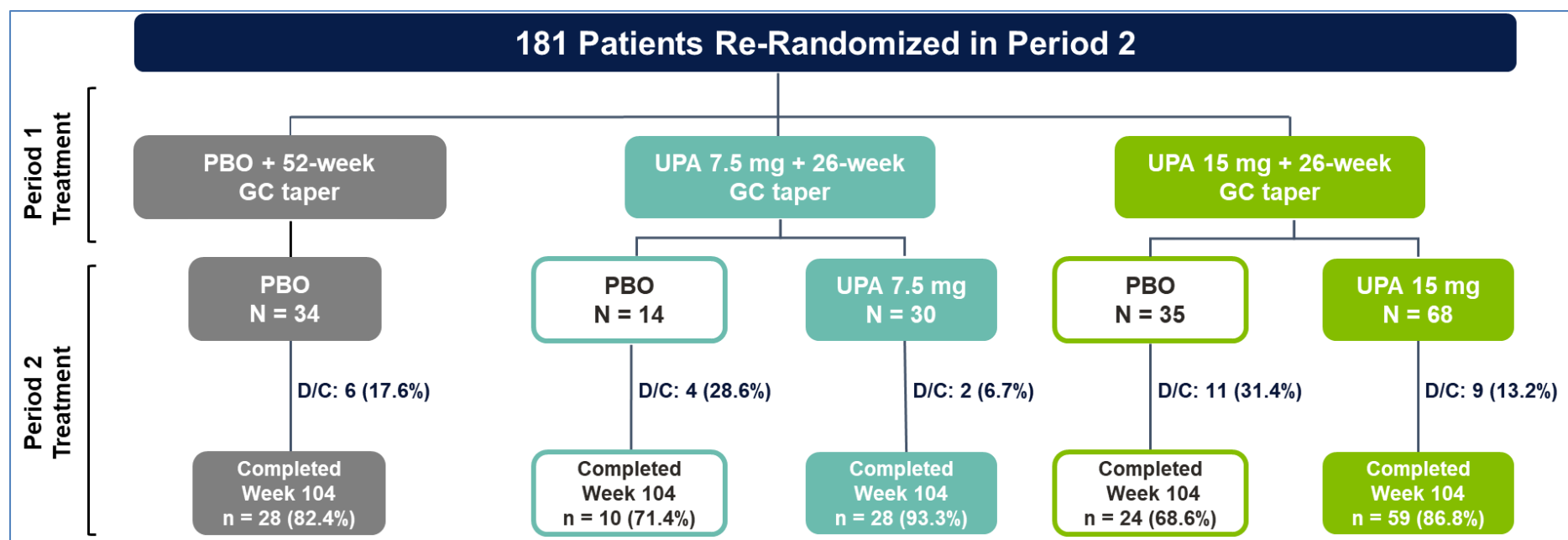


Figure 2. Patient disposition for patients entering Period 2 who achieved sustained remission for ≥ 24 consecutive weeks prior to Week 52

Abbreviations: D/C, discontinued; GC, glucocorticoid; PBO, placebo; UPA, upadacitinib

Table 2. Baseline characteristics of patients entering Period 2 who achieved sustained remission for ≥ 24 consecutive weeks prior to Week 52

Baseline characteristics, n (%) unless specified		PBO + 52-week GC taper $\rightarrow$ PBO N = 34	UPA 15 mg + 26-week GC taper $\rightarrow$ PBO N = 35	UPA 15 mg + 26-week GC taper $\rightarrow$ UPA 15 N = 68
Age (years)	Mean (SD)	<u>70.2 (7.8)</u>	<u>69.9 (6.7)</u>	<u>71.3 (8.2)</u>
	Min, Max	<u>54, 84</u>	<u>56, 82</u>	<u>51, 88</u>
Race	Asian	<u>2 (5.9)</u>	<u>4 (11.4)</u>	<u>4 (5.9)</u>
	White	<u>32 (94.1)</u>	<u>31 (88.6)</u>	<u>64 (94.1)</u>
Disease status	New onset	<u>26 (76.5)</u>	<u>26 (74.3)</u>	<u>49 (72.1)</u>
	Relapsing	<u>8 (23.5)</u>	<u>9 (25.7)</u>	<u>19 (27.9)</u>
Disease duration since diagnosis (days)	New onset, mean (SD)	<u>33.9 (7.5)</u>	<u>39.9 (13.7)</u>	<u>46.0 (45.5)</u>
	Median	<u>34.5</u>	<u>41.0</u>	<u>36.0</u>
	Relapsing, mean (SD)	<u>661.6 (968.5)</u>	<u>931.6 (769.7)</u>	<u>757.4 (770.6)</u>
	Median	<u>161.0</u>	<u>993.0</u>	<u>323.0</u>
GC dose (mg)	Mean (SD)	<u>33.5 (12.3)</u>	<u>32.3 (12.4)</u>	<u>33.1 (12.4)</u>
	Median	<u>30.0</u>	<u>30.0</u>	<u>30.0</u>
ESR (mm/hour)	Mean (SD)	<u>17.5 (19.2)</u>	<u>15.9 (12.8)</u>	<u>20.9 (17.9)</u>
hsCRP (mg/dL)	Median	<u>0.17</u>	<u>0.24</u>	<u>0.26</u>
Prior use of IL-6 inhibitor	Yes	<u>2 (5.9)</u>	<u>4 (11.4)</u>	<u>2 (2.9)</u>

Abbreviations: ESR, erythrocyte sedimentation rate; GC= glucocorticoid; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; PBO, placebo; SD, standard deviation; UPA, upadacitinib

Period 2 efficacy results – R1 (patients who achieved sustained remission for ≥ 24 consecutive weeks prior to Week 52)

Efficacy endpoints

A statistically significantly greater proportion of patients maintained remission when continuing on upadacitinib 15 mg versus those who switched from upadacitinib 15 mg to placebo during Period 2 (67.3% versus 28.6%; $p < 0.0001$ [nominal]) (Figure 3).

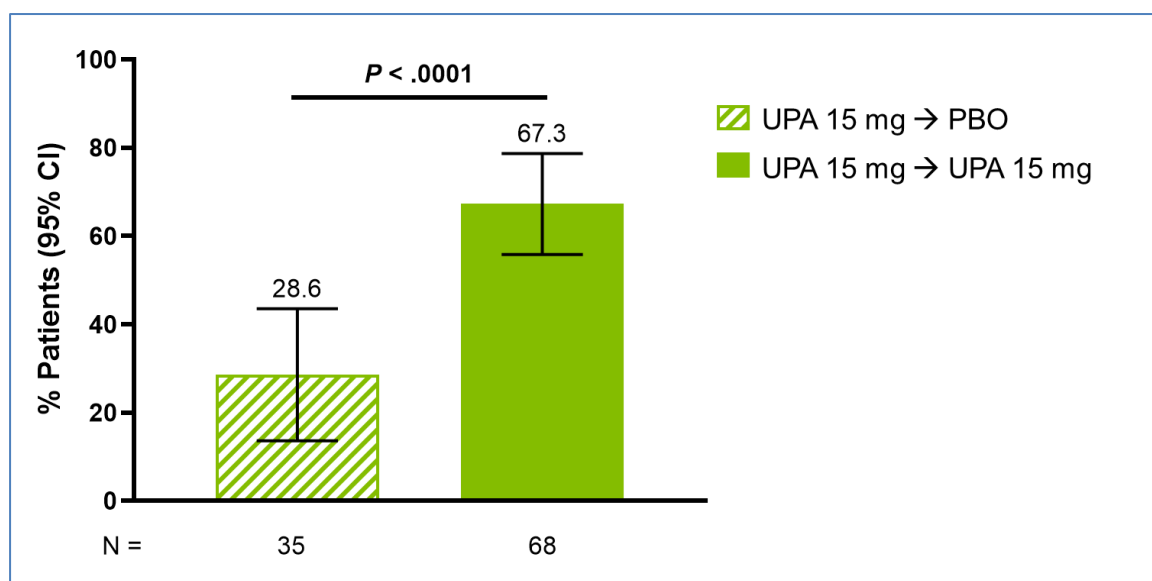


Figure 3. Proportion of patients maintaining remission from Week 52 to Week 104

Abbreviations: CI, confidence interval; PBO, placebo; UPA, upadacitinib
Note: P values are nominal

Sustained complete remission

A statistically significantly higher proportion of patients maintained complete remission when continuing on upadacitinib 15 mg versus those who switched from upadacitinib 15 mg to placebo during Period 2 (71.9% versus 20.0%; p < 0.0001 [nominal]) (Figure 4).

Cumulative corticosteroid exposure

Upadacitinib 15 mg demonstrated a steroid-sparing effect, with a statistically significant reduction in both median and mean cumulative corticosteroid exposure from Week 52 to Week 102 in patients who continued on upadacitinib 15 mg versus those who switched to placebo (median: 0 mg versus 1048 mg; p < 0.0001 [nominal]) (mean: 139.2 mg versus 1532.6 mg) (Figure 5).

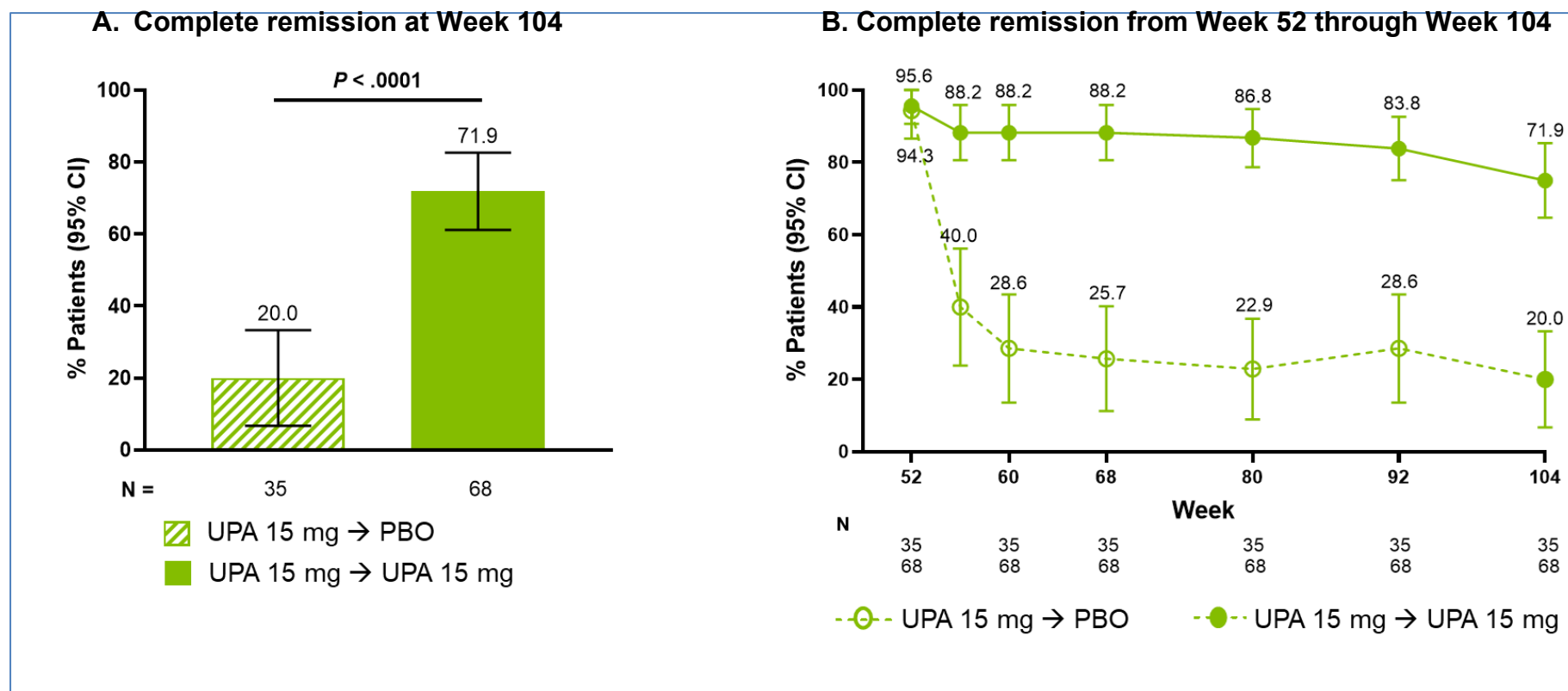


Figure 4. Proportion of patients in complete remission from Week 52 to Week 104

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

Note: P values are nominal

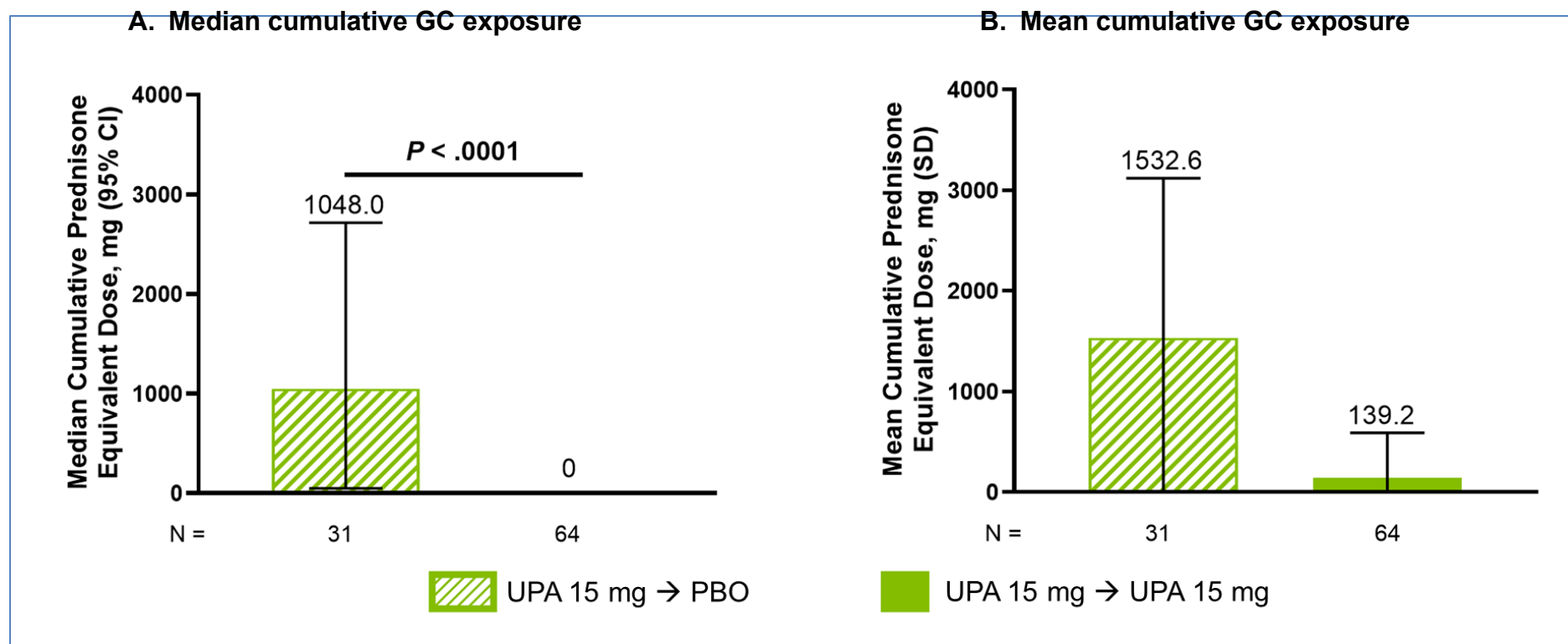


Figure 5. Cumulative GC exposure from Week 52 to Week 104

Abbreviations: CI, confidence interval; GC, glucocorticoid; PBO, placebo; SD, standard deviation; UPA, upadacitinib
 Note: P values are nominal

GCA flares

Statistically significantly lower proportions of patients continuing on upadacitinib 15 mg during Period 2 experienced disease flare versus those who switched from upadacitinib 15 mg to placebo (15.5% versus 59.1%; $p < 0.0001$ [nominal]) (Figure 6).

Risk of disease flare was 90% lower (HR 0.1 [95% CI: 0.04, 0.025]) ($p < 0.0001$ [nominal]) in patients who continued on upadacitinib 15 mg versus those who switched from upadacitinib 15 mg to placebo (Figure 7).

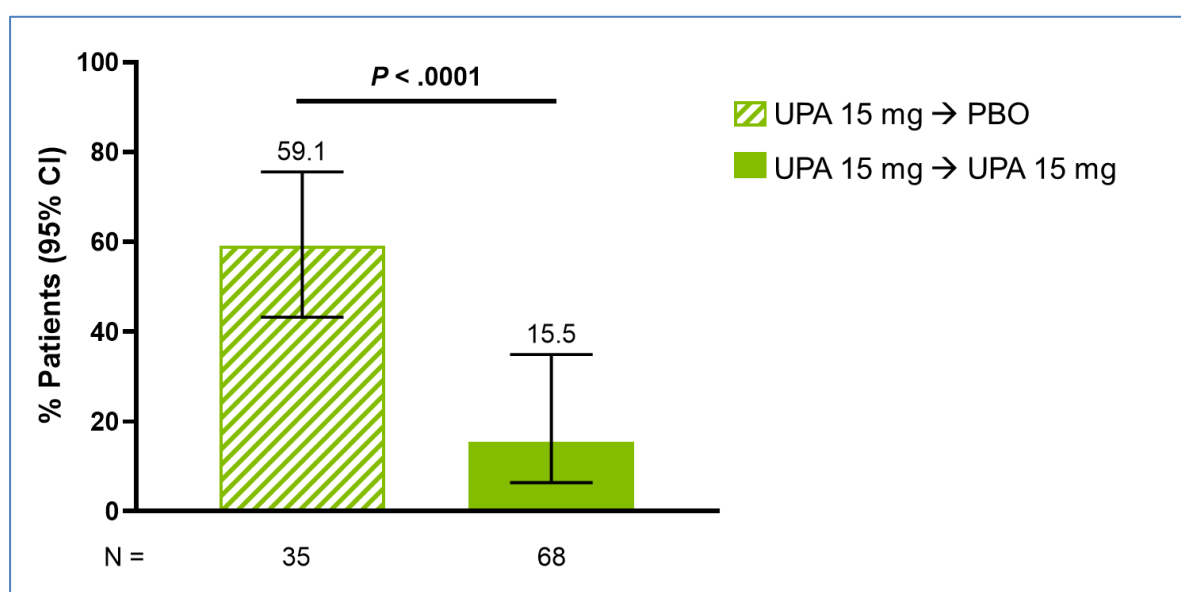


Figure 6. Proportion of patients experiencing ≥ 1 disease flare from Week 52 to Week 104 plus 30 days follow-up

Abbreviations: CI, confidence interval; PBO, placebo; UPA, upadacitinib
Note: P values are nominal

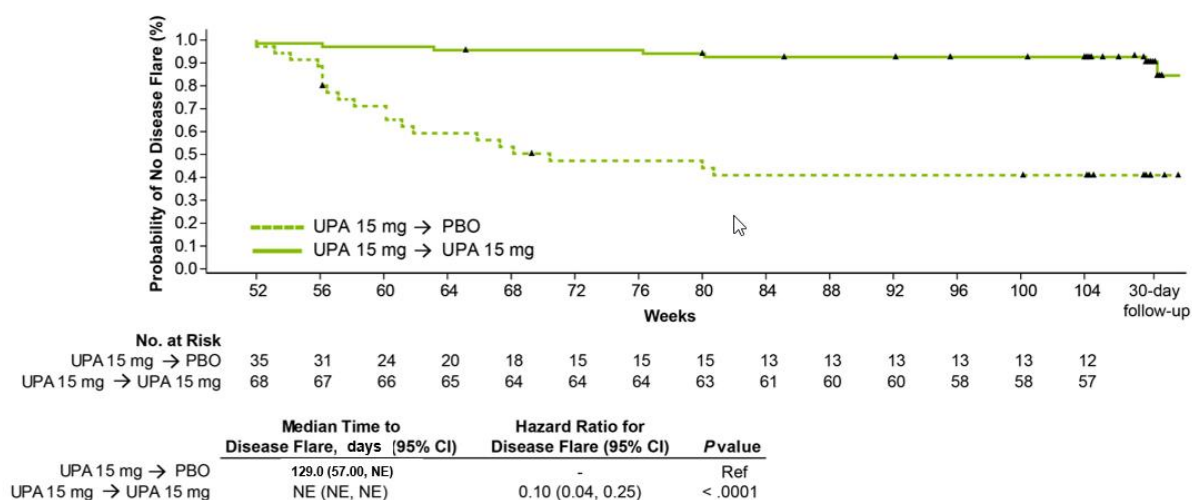


Figure 7. Time to first disease flare from Week 52 to Week 104 plus 30 days follow-up

Abbreviations: NE, not estimable; PBO, placebo; Ref, reference; UPA, upadacitinib
Note: P values are nominal

2-Year Safety Analysis

Safety analysis included all patients enrolled in SELECT-GCA who received ≥ 1 dose of study drug. Upadacitinib 15 mg was generally well-tolerated during Period 2, with the full safety profile consistent with preliminary Period 2 results (SS_LT) and Period 1 (SS1). The proportion of events per 100 patient-years of adverse events leading to study drug discontinuation remained lower in patients who continued on upadacitinib 15 mg versus those who switched to placebo during Period 2 (19.2 [95% CI: 14.4, 25.2] versus 26.1 [95% CI: 18.2, 36.3]) (Table 3). No adverse events of special interest of tuberculosis, gastrointestinal perforation, or lymphoma were reported in any treatment groups (

Table 4).

Table 3. Summary of treatment-emergent adverse event rate through 2 years in SELECT-GCA

	Through 1 Year (Period 1)		Through 2 Years	
Events/100 PY (95% CI) [No. of Events]	PBO + 52-week GC taper (N = 112) (PY = 94.3)	UPA 15 mg + 26-week GC taper (N = 209) (PY = 178.1)	PBO + 52-week GC taper (N = 112) (PY = 133.9)	UPA 15 mg + 26-week GC taper (N = 209) (PY = 270.3)
Any TEAE	748.6 (694.4, 805.9) [706]	817.7 (776.2, 860.8) [1456]	651.9 (609.4, 696.6) [873]	681.0 (650.2, 712.8) [1841]
Serious TEAE	42.4 (30.3, 57.8) [40]	36.5 (28.2, 46.5) [65]	36.6 (27.1, 48.4) [49]	31.1 (24.8, 38.5) [84]
AE leading to study drug discontinuation	32.9 (22.3, 46.7) [31]	23.0 (16.5, 31.2) [41]	26.1 (18.2, 36.3) [35]	19.2 (14.4, 25.2) [52]
Deaths	2.1 (0.3, 7.7) [2]	1.1 (0.1, 4.1) [2]	1.5 (0.2, 5.4) [2]	0.7 ^c (0.1, 2.7) [2]

Abbreviations: AE, adverse event; CI, confidence interval; GC, glucocorticoid; PBO, placebo; PY, patient-years; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

Table 4. Rates of treatment-emergent adverse events of special interest through 2 years in SELECT-GCA

Events/100 PY (95% CI) [No. of Events]	Through 1 Year (Period 1)		Through 2 Years	
	PBO + 52-week GC-T (N = 112) (PY = 94.3)	UPA 15 mg + 26-week GC-T (N = 209) (PY = 178.1)	PBO + 52-week GC-T (N = 112) (PY = 133.9)	UPA 15 mg + 26-week GC-T (N = 209) (PY = 270.3)
Serious infection	<u>12.7</u> (6.6, 22.2) [12]	<u>7.9</u> (4.3, 13.2) [14]	<u>10.5</u> (5.7, 17.5) [14]	<u>5.9</u> (3.4, 9.6) [16]
Opportunistic infection [†]	<u>1.1</u> (0, 5.9) [1]	<u>2.2</u> (0.6, 5.8) [4]	<u>1.5</u> (0.2, 5.4) [2]	<u>1.8</u> (0.6, 4.3) [5]
Herpes zoster	<u>4.2</u> (1.2, 10.9) [4]	<u>7.3</u> (3.9, 12.5) [13]	<u>3.0</u> (0.8, 7.6) [4]	<u>5.9</u> (3.4, 9.6) [16]
CPK elevation	<u>0</u>	<u>3.4</u> (1.2, 7.3) [6]	<u>0</u>	<u>3.3</u> (1.5, 6.3) [9]
Hepatic disorder	<u>6.4</u> (2.3, 13.8) [6]	<u>7.3</u> (3.9, 12.5) [13]	<u>5.2</u> (2.1, 10.8) [7]	<u>5.5</u> (3.1, 9.2) [15]
NMSC [‡]	<u>2.1</u> (0.3, 7.7) [2]	<u>2.8</u> (0.9, 6.6) [5]	<u>3.8</u> (1.2, 8.9) [5]	<u>2.6</u> (1.1, 5.4) [7]
Malignancy excluding NMSC [‡]	<u>2.1</u> (0.3, 7.7) [2]	<u>2.3</u> (0.6, 5.8) [4]	<u>1.5</u> (0.2, 5.4) [2]	<u>1.9</u> (0.6, 4.4) [5]
MACE (adjudicated ‡,§)	<u>2.1</u> (0.3, 7.7) [2]	<u>0</u>	<u>1.5</u> (0.2, 5.4) [2]	<u>0</u>
VTE (adjudicated) ^{‡,¶}	<u>4.3</u> (1.2, 10.9) [4]	<u>3.9</u> (1.6, 8.1) [7]	<u>3.0</u> (0.8, 7.7) [4]	<u>3.0</u> (1.3, 5.8) [8]
Anaemia	<u>3.2</u> (0.7, 9.3) [3]	<u>8.4</u> (4.7, 13.9) [15]	<u>4.5</u> (1.6, 9.8) [6]	<u>8.1</u> (5.1, 12.3) [22]
Lymphopenia	<u>0</u>	<u>2.2</u> (0.6, 5.8) [4]	<u>0.7</u> (0, 4.2) [1]	<u>1.8</u> (0.6, 4.3) [5]
Neutropenia	<u>1.1</u> (0, 5.9) [1]	<u>0</u>	<u>0.7</u> (0, 4.2) [1]	<u>0</u>
Retinal detachment	<u>3.2</u> (0.7, 9.3) [3]	<u>2.2</u> (0.6, 5.8) [4]	<u>3.0</u> (0.8, 7.6) [4]	<u>1.8</u> (0.6, 4.3) [5]
Bone fracture [‡]	<u>6.5</u> (2.4, 14.2) [6]	<u>7.7</u> (4.1, 13.1) [13]	<u>4.7</u> (1.7, 10.1) [6]	<u>6.2</u> (3.6, 10.1) [16]

[†] Excludes herpes zoster.

[‡] Reported as exposure-adjusted incidence (n/100 PY) [no. of patients].

[§] Defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

[¶] Includes pulmonary embolism and deep vein thrombosis.

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; GC, glucocorticoid; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; PY, patient year; UPA, upadacitinib; VTE, venous thromboembolism

Ross Dent
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3 Piccadilly Place
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M1 3BN

CONFIDENTIAL

21st November 2025

Dear Ross,

Upadacitinib in adult patients with giant cell arteritis (GCA) [ID6299]

AbbVie welcomes the opportunity to discuss the appraisal for upadacitinib for treating adult patients with giant cell arteritis (GCA) at the NICE Committee D meeting on 10 December 2025. In response to previous requests from the EAG, we would like to inform you that topline, interim 2-year results from the re-randomised Period 2 portion of the SELECT-GCA Phase 3 trial are now available. This will be submitted as an addendum to the submission on NICE Docs and is also available in published format [here](#).

Please note that while the data are available, it is not possible to fulfil the EAG request for period 2 data in the requested format. An overview of the trial design and the rationale for why this is not possible is outlined below.

SELECT-GCA Study Objectives and Trial Design

As outlined in our company submission (Section 2.3.1), the SELECT-GCA trial was separated into two distinct periods, each with specific objectives and distinct patient populations.

- **Period 1:** To evaluate the efficacy and safety of upadacitinib 7.5 or 15 mg once daily (OD) in combination with a 26-week corticosteroid (CS) taper regimen compared to placebo in combination with a 52-week CS taper regimen in subject with new onset or relapsing GCA, as measured by the proportion of subjects in sustained remission at Week 52.
- **Period 2:** To evaluate the safety and efficacy of continuing versus withdrawing upadacitinib in maintaining remission in subjects who achieved remission in Period 1.

Eligibility for entry into Period 2 required patients to be in remission at the end of Period 1, according to two pre-defined criteria:

- **R1 Population:** Patients who maintained remission for at least 24 consecutive weeks prior to Week 52.
- **R2 Population:** Patients who were in remission at Week 52 but had not met the 24-week sustained remission criterion. Patients who did not meet either R1 or R2 criteria were discontinued from the study at Week 52.

According to the study design (Addendum, Figure 1), eligible patients (R1 population) were then re-randomised (2:1) to either continue receiving upadacitinib 15 mg (UPA15/UPA15) or to stop treatment and switch to placebo (UPA15/PBO). The 2-year topline efficacy results included in the addendum refer to the R1 population, and the safety results are a pooled analysis of both the R1 and R2 populations.

Regarding the EAG's request for specific Period 2 data (fifteen tables and KM curves for time to first flare (TTFF), segmented by ITT, new onset and relapsed subgroups and fifteen tables for time to subsequent flare taking time to first flare as day 0, it is not possible to fulfil this request for three reasons:

- 1) Period 2 trial design re-randomised patients from week 52 to week 104, and therefore, it is not possible to track patients from week 0 through to week 104. As previously mentioned, the objective of Period 2 was to demonstrate the benefit of continuous upadacitinib versus the withdrawal after 1-year.
- 2) Due to the inclusion criteria (i.e., subjects are required to be in sustained remission at Week 52). Period 2 represents a distinct patient population from Period 1, of patients that achieve sustained remission. For this reason, and as previously stated during clarification questions stage, the requested data are not methodologically suitable for determining TTFF across both periods and therefore should not be used to inform model extrapolations.
- 3) Additionally, it would not be possible to estimate the time to subsequent flare by pooling both periods and using the first flare date as Day 0, as for patients to have a "subsequent flare" they need to re-meet the flare criteria.

In summary, Period 2 of SELECT-GCA was designed to evaluate the safety and efficacy of continuing versus withdrawing upadacitinib. The interim data from Period 2 demonstrates the significant and maintained steroid sparing effect of upadacitinib when continued beyond 1 year, with higher rates of sustained and complete remission, fewer flares and significant reduction in steroids compared with those who withdrew from upadacitinib to placebo at Week 52.

Thank you for your time and please do not hesitate to contact me using the details below if you would like to discuss this further.

Yours sincerely,

[Redacted signature block]

APPENDIX

Table 1. Key differences between Period and 1 Period 2 SELECT-GCA study

	SELECT-GCA	
	Period 1 (Week 0 to Week 52, n=428)	Period 2 (Week 52 to Week 104, n=181)
Study objective(s)	To evaluate the efficacy and safety of upadacitinib 7.5 (UPA7.5) or 15 mg (UPA15) once daily (OD) in combination with a 26-week corticosteroid (CS) taper regimen compared to placebo in combination with a 52-week CS taper regimen in subject with new onset or relapsing GCA, as measured by the proportion of subjects in sustained remission at Week 52.	To evaluate the safety and efficacy of continuing versus withdrawing upadacitinib in maintaining remission in subjects who achieved remission in Period 1.
Population	Adults ≥ 50 years with active new onset or relapsing GCA	Patients in remission for ≥ 24 consecutive weeks before the week 52 visit. Patients who were in remission at Week 52 but not 24 consecutive weeks prior to Week 52. Any patients not meeting either the R1 or R2 criteria for remission were discontinued from the study at Week 52.
Intervention	Upadacitinib (daily oral tablet) with a 26-week CS taper regimen	Eligible patients receive upadacitinib (daily oral tablet). Dose is according to what patients originally received during Period 1.
Comparator(s)	Placebo with a 52-week CS taper regimen	Eligible patients either continue the same dose of UPA received during P1 (UPA/UPA) or switch to PBO in period 2 (UPA/PBO). Eligible patients originally randomized to PBO continued PBO.
Key eligibility criteria	Adult male or female ≥50 years of age Diagnosis of GCA according to the following criteria: - History of ESR ≥50 mm/hour or hsCRP ≥1.0 mg/dL - Presence of at least either unequivocal cranial symptoms of GCA, or unequivocal symptoms of PMR. - Presence of at least one of either temporal artery biopsy revealing features of GCA, or evidence of large vessel vasculitis by angiography or cross-sectional imaging. Active GCA, either new onset or relapsing, within 8 weeks of baseline.	R1: Patients in remission (absence of the signs or symptoms of GCA and adherence to the protocol-defined GC taper) for ≥ 24 consecutive weeks before the week 52 visit. R2: Patients who were in remission at Week 52 but not 24 consecutive weeks prior to Week 52. Any patients not meeting either the R1 or R2 criteria for remission were discontinued from the study at Week 52.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Upadacitinib for giant cell arteritis [ID6299]

Summary of Information for Patients (SIP)

May 2025

File name	Version	Contains confidential information	Date
[ID6299] Upadacitinib SIP	1.0	No	28 May 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

Note: explanations of terms in **bold** are available in the glossary (section 4b) to aid the reader.

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Upadacitinib (Rinvoq®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults with giant cell arteritis

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The **marketing authorisation** is a license that enables a drug to be sold; it is only granted after assessing and reviewing all the evidence for that treatment. Upadacitinib (RINVOQ®) is anticipated to be indicated for the treatment of giant cell arteritis (GCA) in adult patients. A type II variation application for the **marketing authorisation** has been submitted to the UK Medicines & Healthcare products Regulatory Agency (MHRA) to extend the therapeutic indication to include GCA. The Committee for Medicinal Products for Human Use (CHMP) gave positive opinion on 27 February 2025. A type II variation application for the **marketing authorisation** to extend the therapeutic indication to include GCA was granted by the European Commission on 7 April 2025.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AbbVie collaborates and engages with patient groups supporting people with giant cell arteritis.

Where this includes any Transfer of Value, for example to support the development of information for patients and their families, this is declared on an annual basis and is available at: <https://www.abbvie.co.uk/our-company/policies-disclosures.html>

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is GCA?

Giant cell arteritis (GCA), previously known as temporal arteritis, is a condition where the blood vessels become swollen due to **inflammation**.¹⁻³ The blood vessels involved include those in the head and neck, and in some case the aorta, the main artery that carries blood from the heart.¹⁻³ This **inflammation** leads to symptoms such as headaches, scalp tenderness, jaw pain while chewing, vision problems (such as double vision or sudden vision loss), fatigue, fever, and weight loss. If left untreated, GCA can lead to serious complications like blindness, stroke, or a dangerous swelling of a section of an artery, commonly referred to as an aneurysm.⁴⁻⁷

Giant cell arteritis is considered a medical emergency and it is important to treat quickly with corticosteroids to reduce inflammation and prevent permanent damage such as blindness and stroke.⁸⁻¹¹ The aim of treatment is to control the disease and achieve steroid-free **remission**, which is where the symptoms become less severe and the patient no longer shows signs of active disease.^{12,13} However, long-term corticosteroid treatment is linked to serious **side-effects**, including cataracts, high blood pressure, heart failure, type 2 diabetes mellitus, bone disease, and infections.¹⁴⁻²⁰ Therefore, once symptoms are controlled the corticosteroid dose is then gradually reduced over time with aim to stop treatment, a process that can take years.^{12,13} The dose must be reduced slowly, as reducing the dose too quickly puts a patient at risk of disease **relapse**, where the disease becomes worse after a period of improvement, and signs and symptoms of disease return.^{12,13} Patients often require repeated and long-term corticosteroid treatment for 2 years, and in some cases as long as 8 years.²¹⁻²⁴ Some patients may never stop corticosteroid treatment. Unfortunately, **relapse** is common even with gradual dose reductions, and treatment for **relapse** requires an increase in corticosteroid dose. Approximately 50% of patients experience **relapse**, often in the first year of diagnosis.^{22,23,25-27} Consequently, over time patients receive increasingly high total amounts of corticosteroids, which increases the risk of serious **side-effects**.^{19-21,28}

How many people are living with GCA in the UK?

Giant cell arteritis mostly affects adults over 50 years of age, and is more common in women and in Caucasians of Northern European or Scandinavian descent.^{29,30} It is estimated that GCA affects 273 people per 100,000 individuals over 50 years of age in the UK.³¹

How does GCA affect patients?

Patients with GCA suffer from reduced quality-of-life, both due to the symptoms of the disease and the serious **side-effects** associated with increasingly high total amounts of corticosteroids received over time.³²⁻³⁴ Symptoms such as fatigue and pain affect everyday life, restricting a patients ability to work or take part in social and leisure activities, and to perform household tasks

or personal care.^{34,35} This leads to a loss of independence for patients that can be devastating.³⁶ Vision loss is a feared symptom of GCA, which leaves patients feeling vulnerable and often struggling to cope, and is linked to worse quality-of-life.^{2,35,37-39}

Patients with GCA have an increased risk of other serious conditions such as heart attacks and stroke due to numerous aspects of the disease.^{7,40} Patients with GCA are 4 times more likely than those without GCA to have a heart attack, 1.5 times more likely to have a stroke, and more than 3 times more likely to have an aortic aneurysm, which can tear and become life-threatening.^{6,40,41} The first year after diagnosis is a particularly high-risk period for patients, with a 1.5 times higher risk of death for patients.⁴²

Corticosteroids are the main treatment for patients with GCA. Patients will often need to take corticosteroids every day for a long time – often for 2 years or more. The consistent long-term use of corticosteroids leads to patients receiving increasingly high total amounts over time, which is associated with serious **side-effects**.^{1,21} An estimated 83% of patients with GCA experience **side-effects** due to corticosteroid treatment. The most common **side-effects** include cataracts, high blood pressure, heart failure, type 2 diabetes mellitus, bone disease, and infections,¹⁴⁻²⁰ which can be linked to the development of other diseases or put patients at risk of injury.⁴³ Furthermore, **side-effects** associated with corticosteroid have a serious impact on patient mental health.³⁶ Almost half of patients with GCA show signs of anxiety or depression, and one third report serious mental impacts due to GCA.^{36,44}

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The diagnosis of GCA is based on a doctor's assessment of the disease signs and symptoms, and laboratory and imaging tests. However, since GCA is considered a medical emergency, patients should be treated with high-dose corticosteroids on suspicion of GCA, with diagnosis confirmed once treatment has started.^{12,13} When a patient is first diagnosed with GCA, this is called '**new onset**' disease. When a patient's disease becomes worse after a period of improvement, and signs and symptoms return, this is called '**relapsing**' disease.

Diagnosis of GCA can be complicated, as different patients may present with different signs and symptoms. Some diagnostic tests include examination by a doctor for tenderness around the scalp and temples, blood pressure measurements, blood vessel imaging techniques, and laboratory tests for inflammatory markers.^{12,13}

The introduction of upadacitinib as a new treatment for patients with GCA would not require additional diagnostic tests.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The aim of GCA treatment is to prevent vision loss and achieve **remission**, a state where the patient no longer shows signs or symptoms of active disease.^{12,13} Patients have limited treatment options, with high dose corticosteroids as the main treatment. Patients receive initial corticosteroids to achieve **remission**, the dose is then gradually reduced over time with the aim to stop treatment, a process that can take years.^{12,13} Patients often require repeated and long-term corticosteroid treatment for 2 years, and in some cases as long as 8 years.²¹⁻²⁴ Some patients may never stop corticosteroid treatment. Consequently, over time patients can receive increasingly high total amounts of corticosteroids, which are associated with serious **side-effects**, including cataracts, high blood pressure, heart failure, type 2 diabetes mellitus, bone disease, and infections,¹⁴⁻²⁰ particularly in this predominantly older population.^{19,45} Unfortunately, despite corticosteroid treatment, **relapse** is estimated to occur in 50% of patients, which is where the disease becomes worse after a period of improvement and signs and symptoms of the disease return.^{22,23,25-27} Of the patients who **relapse**, many do so in the first year of treatment.^{22,25} **Relapse** requires an increase in corticosteroid dose, which exposes patients to ever increasing total amounts of corticosteroid and greater risk of associated **side-effects**.⁴⁶

The only alternative treatment available to patients is tocilizumab, a drug given every week by injection.⁴⁷ Injections can be challenging for some patients, particularly older patients.⁴⁸ In England, tocilizumab is only approved in patients with **relapsing** GCA.⁴⁹ However, these patients can only receive tocilizumab for up to a maximum of 1 year. After a year patients are no longer eligible for treatment and if the disease relapses, they return to corticosteroid treatment.^{12,13} A UK study (TOC STOP) found that 6 months after stopping tocilizumab, 21% of patients had **relapsed**, and after 2 years, 49% of patients had **relapsed**. These patients needed an increase in corticosteroid dose to control their disease.⁵⁰ When doctors were asked about tocilizumab use in England they emphasised that its use in England is limited, and as such corticosteroids are considered the main treatment for GCA patients.

An unmet need exists for alternative long-term treatments in patients with GCA that are effective, well-tolerated, and reduce the total amount of corticosteroids required to control disease and minimise the associated **side-effects**. This is emphasised by NHS England Specialised Commissioning (NHSE), the body responsible for planning and funding healthcare services across England, who stated '*there is enormous unmet need for people with GCA*', and the British Society of Rheumatology '*an area of significant unmet need*'.⁵¹ In line with clinical expert opinion, upadacitinib has the potential to be a vital alternative long-term treatment and reduce the total amount of corticosteroids required to control disease and the associated **side-effects**. Furthermore, upadacitinib is conveniently taken by mouth and has a new mechanism of action compared with current treatments, providing patients with a valuable alternative.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for

collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Giant cell arteritis is a long-term condition for which the symptoms and treatment severely impact patients' quality-of-life. Interviews conducted with UK patients highlighted how widely the disease impacts daily life, with symptoms of GCA and **side effects** of treatment restricting a patient's ability to work, take part in hobbies, carry out personal care, and maintain relationships, and damaging a patient's financial circumstances. In particular, patients found it difficult to cope with the long-term ongoing symptoms and **side effects**, and described the disease as being '*life-changing*' and '*restricting my life totally*'.³⁵ In another series of interviews conducted with UK and Australian patients the disease was shown to impact daily living and function, participation in relationships, patient's mental or psychological wellbeing, and their sense of self.³⁴

In a quality-of-life survey assessing the physical and mental health of patients with GCA, 76% reported experiencing physical disability, while 63% identified mental disability due to their condition. Among these, 46% indicated their condition resulted in moderate-to-severe physical disability, and 33% reported moderate-to-severe mental disability.³⁶

A loss of normality in day-to-day living and loss of independence are recurring themes across studies, and are linked to poorer mental health.³⁴⁻³⁶ Fears around vision loss are common, and ranked by many patients as the most concerning symptom of GCA.³² Vision loss is a devastating symptom that is difficult to cope with and reduces both a patient's physical functioning and their mental health.^{38,39} Patients may need additional support from family caregivers to deal with the symptoms and treatment **side-effects** of GCA, who spend an average of 19 hours per week in caregiving activities.⁵²

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Upadacitinib is a treatment designed to block certain proteins in the body called **Janus kinases** (JAKs), which play an important role in inflammation and immune responses.⁵³ **Janus kinases** help transmit signals within cells that tell them to grow, divide, or act in certain ways,⁵³ and are implicated in the development of GCA.^{1,54-56} There are four types of JAKs (JAK1, JAK2, JAK3, and TYK2), and upadacitinib is selective in blocking JAK1 more effectively than the other three types.⁵⁷ Upadacitinib blockade of JAK1 stops multiple inflammatory pathways that are implicated in GCA.⁵³ This could make it more effective at reducing inflammation in patients with GCA compared with corticosteroids, which work in a broad and non-specific way.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Upadacitinib is anticipated to be used in combination with corticosteroids, with the dose of corticosteroids reduced over time in accordance with standard clinical practice.⁵⁷ Corticosteroids are used to quickly treat symptoms of GCA and reduce the risk of vision loss. However, corticosteroids are linked to serious **side-effects**, including cataracts, high blood pressure, heart failure, type 2 diabetes mellitus, bone disease, and infections.¹⁴⁻²⁰ Once symptoms are controlled, the dose of corticosteroid should be reduced until it is safe to stop the corticosteroids.^{12,13,19,45} Upadacitinib use is anticipated to be continued after corticosteroids are stopped; reflecting the chronic nature of giant cell arteritis. The duration of upadacitinib treatment should be guided by disease activity, physician discretion, and patient choice.⁵⁷

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Upadacitinib is a pill taken by mouth daily. Upadacitinib is anticipated to be used in combination with corticosteroids, with the dose of corticosteroids reduced over time in accordance with standard clinical practice.⁵⁷ Upadacitinib use is anticipated to be continued after corticosteroids are stopped reflecting the chronic nature of GCA. The duration of treatment should be guided by disease activity, physician discretion, and patient choice.⁵⁷

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The SELECT-GCA (NCT03725202) Phase 3, multi-national trial provides evidence for the **efficacy** (how well the treatment works) of upadacitinib in patients with **new onset** or **relapsing** (where the disease become worse again after a period of improvement) GCA.^{58,59} The trial also provides evidence on the safety profile of upadacitinib. Most of the patients in the SELECT-GCA trial were from Europe (including the UK).^{58,59}

The SELECT-GCA trial was randomised, double-blind, **placebo**-controlled, which means the patients were randomly assigned to receive either medication or **placebo** (an inactive substance used to compare to an active medication), and neither the patient nor doctor knew which treatment they were receiving.^{58,59} The trial compared upadacitinib in combination with a reduction in corticosteroid dose over 26-weeks, versus **placebo** in combination with a slower reduction in corticosteroid dose over 52-weeks.^{58,59}

The SELECT-GCA trial included 210 patients who received 15 mg of upadacitinib and 105 patients who received **placebo**, both administered as a pill by mouth daily. To be enrolled in the trial patients had to be:^{58,59}

- Adult male or female 50 years of age or over
- Diagnosed with active GCA, either **new onset** or **relapsing**

- Received treatment with 40 mg or more of corticosteroid at any time prior to the trial start and be receiving 20 mg or more of corticosteroids at the trial start

The **efficacy** of treatment was measured by:^{58,59}

- Disease **remission** – the main measure of **efficacy** was the number of patients who were able to achieve **remission**, i.e., showed no disease signs or symptoms and adhered to the planned reduction in corticosteroid dose over time
- Total corticosteroid dose – the total amount of corticosteroids required by a patient to control disease over the course of the trial
- GCA **flares** – the number of patients who experienced a disease **flare**, the length of time to disease **flare**, and the number of disease **flares** per patient
- Assessment of patient quality of life

The SELECT-GCA trial begun in 2019 and concluded in March 2025. The results in the company submission are those most recently available (February 2024),⁵⁸ and have also been published in an international medical journal.⁵⁹

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The SELECT-GCA trial showed that upadacitinib, with a reduction in corticosteroids over 26-weeks, worked better at treating patients with GCA compared with **placebo** and a slower reduction in corticosteroids over 52-weeks. The main results are as follows:

Disease remission

Significantly more patients treated with upadacitinib stayed in **remission**, meaning they had no signs or symptoms of GCA and successfully followed the planned reduction in corticosteroid dose over time, compared to those who received **placebo**.^{58,59}

Corticosteroid dose

Upadacitinib helped reduce the total amount of corticosteroids required to control disease over the course of the trial, as many patients were able to manage with lower doses compared with those who received a **placebo**.^{58,59}

Giant cell arteritis flares

Upadacitinib reduced the number of patients who had a GCA **flare** compared with those who received a **placebo**.^{58,59} In patients who did experience a GCA **flare**, upadacitinib helped delay the time to disease **flare** compared with **placebo**.^{58,59} Furthermore, overall upadacitinib reduced the number of disease **flares** per patient compared with placebo.^{58,59}

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Patients with GCA suffer from reduced quality of life due to the symptoms of GCA and the **side effects** of corticosteroid treatment. The impact of upadacitinib on patient quality of life was assessed in SELECT-GCA using several patient surveys that are typically used to measure the impact of disease.^{58,59} These included the Short Form Health Survey (SF-36) Physical Component Summary (PCS), designed to measure a patient's physical health and functioning, and the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale, that measures fatigue and impact on daily activities and function. A significant improvement in both measures was seen in patients treated with upadacitinib compared to those treated with **placebo**, demonstrating the positive impact that upadacitinib has on patients quality of life.^{58,59}

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In the SELECT-GCA trial upadacitinib was generally well-tolerated, with a safety profile similar to the known safety profile derived from previous upadacitinib studies (equivalent to over 15,000 years of patients on treatment).⁵⁸⁻⁶¹

Side-effects, including those related to the treatment and serious **side-effects**, were reported by a similar number of patients who were treated with upadacitinib and those who received the **placebo**.^{58,59} Most **side-effects** were mild in severity, with less patients stopping upadacitinib treatment due these **side-effects** compared with those who received **placebo**.^{58,59}

Common **side-effects** in patients treated with either upadacitinib or **placebo** were worsening of GCA, headache, high blood pressure, COVID-19 (the trial was conducted during the COVID 19 pandemic and the infection is not reasonably associated with upadacitinib), joint pain, urinary tract infection, back pain, common cold, upper respiratory infection, and diarrhoea.^{58,59}

Side-effects of special interest identified based on the safety profile reported for other **JAK inhibitors**, the class of medication that includes upadacitinib, include heart problems and blood clots. In the SELECT-GCA trial a small number of patients experienced non-fatal blood clots, which was similar between those who received upadacitinib (3.3%) and **placebo** (3.6%). No major heart problems were seen in patients who received upadacitinib, but two cases (1.8%) occurred in those who received **placebo**.^{58,59}

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Patient need

Giant cell arteritis is a serious condition that needs immediate medical attention as it can lead to permanent vision loss and severe cardiovascular-related issues including heart attack and stroke.¹ However, current treatment options remain limited, often accompanied by **side-effects**, and a high risk of disease **relapse**.¹⁹ Upadacitinib would provide a vital alternative long-term treatment that reduces the total amount of corticosteroids required to control disease, helping to minimise the occurrence of associated **side-effects**.

Efficacy

The SELECT-GCA trial demonstrate upadacitinib was more effective in comparison with **placebo** in treating patients with GCA.^{58,59} Significantly more patients treated with upadacitinib stayed in **remission**, with a reduction in the number and delay in time to GCA **flare**, and a reduction in the total amount of corticosteroids required over the course of the trial, compared with **placebo**.^{58,59}

Safety

Upadacitinib was well-tolerated in the SELECT-GCA trial,^{58,59} with a safety profile generally similar with the known safety profile derived from previous upadacitinib studies (equivalent to over 15,000 years of patients on treatment).⁵⁸⁻⁶¹ A similar number of **side-effects** were reported between patients treated with upadacitinib and **placebo**.^{58,59}

Method of administration

Upadacitinib is a pill taken by mouth once daily, a convenient treatment option for patients that does not require them to be trained by a healthcare professional, as opposed to administration of injectables, and does not require specialised storage conditions e.g., refrigeration.

Infection management

Upadacitinib is removed from the body relatively quickly (hours),⁵⁷ which is beneficial when a patients develop a serious infection; upadacitinib treatment can be stopped to enable the immune system to recover and fight the infection.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Janus kinase inhibitors, the class of medication that includes upadacitinib, have been associated with the occurrence of heart problems and blood clots; primarily based on studies of other **Janus kinase inhibitors** in rheumatoid arthritis.⁶² However, upadacitinib was well-tolerated in the SELECT-GCA trial,^{58,59} with a safety profile generally similar with the known safety profile derived from previous upadacitinib studies (equivalent to over 15,000 years of patients on treatment).⁵⁸⁻⁶¹ Specifically, a small number of patients who received both upadacitinib (3.3%) and **placebo** (3.6%) experienced non-fatal blood clots, with no major heart problems seen in patients who received upadacitinib, but two cases (1.8%) occurred in those who received **placebo**.⁵⁸

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects GCA

An economic model has been used to assess the value of upadacitinib for patients with GCA to the NHS. The economic model estimates long-term clinical and economic cost benefits (known as the '**cost-effectiveness**') of using upadacitinib compared with corticosteroids for all GCA patients.

The model separates patients into four groups:

- patients with GCA who are in **remission**, and have not yet experienced a **flare**
- patients with GCA who are experiencing a flare
- patients with GCA who have previously experienced a flare, but are now in **remission**
- patients who have died from either GCA or other causes

The movement of patients between groups reflects a patient's real-world experience of GCA as they move between **remission** and **flare**. Movement between groups is modelled using probabilities that are calculated from patients' time-to-first flare data from the SELECT-GCA trial.

A patient who has not experienced a **flare** enters the model in the pre-flare **remission** group. Once a patient has experienced a **flare**, they can keep experiencing **flares**, moving between the **flare** and post-flare **remission** groups until death.

For each group, costs are applied to each patient for their treatment, healthcare visits associated with GCA, and for the costs of corticosteroid associated **side-effects**. The model considers patients over their whole lifetime.

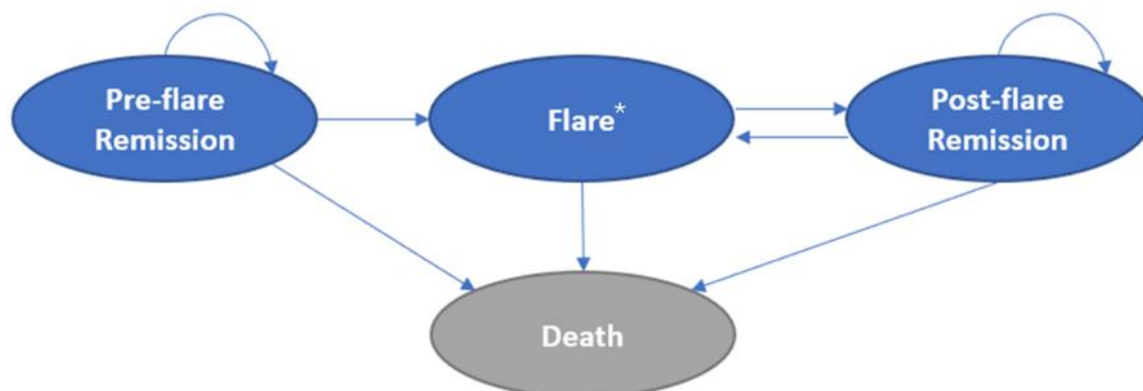


Figure 1. Overview of model structure used to assess the cost-effectiveness of upadacitinib in patients with GCA

Modelling how much upadacitinib extends life

During the SELECT-GCA trial, very few patients died, and the number of patients who died was similar between those treated with upadacitinib and those without. Other studies have reported that patients with GCA have an increased risk of death, particularly in the first year after diagnosis, compared with the general population due to serious complications or corticosteroid associated **side-effects**. The model used this data to reflect the reduced life expectancy that may be expected for patients with GCA.

Modelling how much upadacitinib improves quality of life

The impact that upadacitinib has on patients' quality-of life and life expectancy is described using a measurement called **quality-adjusted life years (QALYs)**, where one QALY describes one year of the patient being in perfect health. Data informing **QALYs** was collected in SELECT-GCA trial using a patient questionnaire called EQ-5D-5L. The questionnaire gathers information on patients' mobility, self-care, and ability to perform daily activities, as well as the presence and severity of pain, discomfort, anxiety, and depression. In addition, the impact of GCA complications, long-term corticosteroid and JAK inhibitor associated **side-effects** upon patient QALYs are captured. Overall, the economic model showed that **QALYs** were improved in patients who received upadacitinib treatment compared with placebo (corticosteroids), due to a reduction in the number of flares and long-term corticosteroid treatment. This is reflected in a comparative improvement to patient's length and quality of life after receiving treatment.

Modelling how the costs of treatment differ with upadacitinib

To estimate the costs of treating GCA, the costs of upadacitinib and corticosteroids, and the costs of managing and monitoring GCA, such as doctor appointments and laboratory tests, are included in the model. In addition, the costs of GCA complications such as vision loss, heart attack, or stroke, the costs of corticosteroid associated **side-effects** such as diabetes, infections, cataracts, and high blood pressure, and JAK inhibitor associated **side-effects** including heart problems and blood clots were included to cover the full costs of treating GCA.

Uncertainty

During the development of an economic model, companies are required to make assumptions where there is a lack of available evidence. The main data source for the model is the SELECT-GCA trial, which ran over 52-weeks. To predict the effects beyond 52-weeks, the company used assumptions, guided by advice from doctors, on the long-term trends in patients with GCA in the real world. These assumptions were changed in a sensitivity analysis to see the impact on the economic model. The results showed that changing these assumptions did not affect the cost-effectiveness results.

Additional factors

Treatment with upadacitinib has additional benefits for patients and their families that may not be captured in the economic model. Patients with GCA experience symptoms and long-term corticosteroid associated **side-effects** that impact their day-to-day life, including work, leisure activities, personal care, household tasks, and personal relationships. Many patients with GCA report a loss of normality, reduced physical independence, and losing their sense of self.³⁴⁻³⁶ While

these factors may not be fully reflected in quality of life measures, easing the burden of disease and restoring a sense of normality can provide significant benefits to patients.

The economic model did not consider the burden on caregivers who care for a friend or family member with GCA, as this is not normally included in NICE decision making. Caregivers for patients with GCA face disruptions to their daily routines and the emotional distress of facing the serious risks associated with GCA. Many patients with GCA are older, and their caregivers are often partners of a similar age, which adds further challenges to caregiving activities. A treatment that sustains **remission** and prevents **relapse** may reduce the burden to caregivers, allowing them to return to normal life, and may reduce their anxieties around disease risks, improving their mental health.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

New mechanism of action

Upadacitinib would provide a vital alternative long-term treatment, conveniently taken by mouth, with a new mechanism of action compared to currently available treatments. Upadacitinib helps reduce **inflammation** by blocking a specific part of the immune system called **Janus kinase 1** (JAK1), which is involved in sending signals that trigger **inflammation**. By stopping these signals, upadacitinib helps reduce the **inflammation** of the blood vessels in GCA.^{53,56,57}

Reduces the total amount of corticosteroids required to control disease

Patients with GCA often require repeated and long-term corticosteroid treatment for 2 years, and in some cases, up to 8 years.²¹⁻²⁴ Over time patients can receive increasingly high total amounts of corticosteroids.⁴⁶ Importantly, the higher the total amount of corticosteroids the greater the risk of serious **side-effects**.^{19-21,28} Upadacitinib has the potential to reduce the total amount of corticosteroids required to control disease and prevent these **side-effects**. In the SELECT-GCA trial upadacitinib helped reduce the total amount of corticosteroids required to control disease, as many patients were able to manage with lower amounts compared with those who received a **placebo**.^{58,59}

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

There are limited approved treatments for patients with GCA. Patients affected by GCA include people with protected characteristics, such as the elderly and those with potential disabilities, including vision loss due to disease complications. The use of upadacitinib is not anticipated to result in equality issues in GCA.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on GCA may be found here:

- Polymyalgia Rheumatica and Giant Cell Arteritis UK – [About giant cell arteritis](#)
- Versus Arthritis – [What is giant cell arteritis](#)
- NHS – [Temporal arteritis](#)

Further information on the SELECT-GCA trial may be found here:

- Clinicaltrials.gov – [SELECT-GCA trial](#)
- New England Journal of Medicine - [SELECT-GCA trial](#)

Further information on NICE and the role of patients can be found here:

- Public Involvement at NICE [Public involvement](#) | [NICE and the public](#) | [NICE Communities](#) | [About](#) | [NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance](#) | [Help us develop guidance](#) | [Support for voluntary and community sector \(VCS\) organisations](#) | [Public involvement](#) | [NICE and the public](#) | [NICE Communities](#) | [About](#) | [NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **Cost-effectiveness:** how effective a drug is in relation to its cost
- **Efficacy:** how well a treatment works
- **Flare:** which is where the patient **relapses**, or where measurements of inflammatory markers increase, requiring an increase in corticosteroid dose
- **Inflammation:** inflammation is your body's way of responding to injury, infection, or irritation. However, when inflammation occurs for a long time or is directed against our own body, it can be harmful
- **Janus kinase (JAK):** a family of enzymes within the body that are part of the immune system
- **Janus kinase inhibitors (JAKi):** a type of drug that stops Janus kinase enzymes from working properly, reducing inflammation

- **Marketing authorisation:** a license that enables a drug to be sold; it is only granted after assessing and reviewing all of the evidence for that drug
- **New onset:** when a patient is first diagnosed with disease
- **Placebo:** an inactive substance that looks identical to a real medication and is taken in the same way
- **Quality-adjusted life years (QALYs):** a measure of both how long and how well someone lives, especially when looking at the impact of healthcare treatments
- **Remission:** a state where the patient no longer shows signs or symptoms of active GCA
- **Relapse/relapsing:** recurrence of GCA signs or symptoms, or an increase in inflammatory markers, requiring an increase of corticosteroid dose (can be used interchangeable with flare)
- **Side-effect:** a medical issues experienced by patients during treatment which is not always linked to the treatment

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Upadacitinib for treating giant cell arteritis [ID6299]

Clarification questions

June 2025

File name	Version	Contains confidential information	Date
ID6299 upadacitinib EAG clarification questions 2025-06- 12 [CON].docx	2	Yes	09 July 2025

Abbreviations:

AEs	adverse events
AO	As observed
BSR	British Society for Rheumatology
CPRD	Clinical Practice Research Datalink
CS	corticosteroid
CSR	clinical study report
CS-T	corticosteroid taper
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D-5L	EuroQoL Five Dimensions Five Levels Questionnaire
ESR	erythrocyte sedimentation rate
FAS	full analysis set
GC	glucocorticoids
GCA	Giant Cell Arteritis
GIRFT	Getting it Right First Time
GPM	general population mortality
HCRU	Healthcare Resource Utilisation
ICD-10	International Classification of Diseases, 10 th Revision
ITC	indirect treatment comparison
ITT	intention-to-treat
KM	Kaplan-Meier
LVV	Large vessel vasculitis
MAIC	matching-adjusted indirect comparison
NICE	National Institute for Health and Care Excellence
PBO	placebo
PMR	polymyalgia rheumatica
RCT	randomised controlled trial
RWE	real-world evidence
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SLR	systematic literature review
SmPC	summary of product characteristics
TA	technology appraisal
TCZ	tocilizumab
TTSF	time-to-subsequent flare
UK	United Kingdom
UPA	upadacitinib
WK	week

Section A: Clarification on effectiveness data

A1. Priority question. Please explain why an indirect treatment comparison (ITC) was not undertaken to compare upadacitinib with tocilizumab for treatment of adult patients with relapsing/refractory giant cell arteritis (GCA), given that the latter was a treatment recommended by NICE for this patient population. Would the company be able to supply an ITC covering key clinical effectiveness outcomes that are used to inform cost-effectiveness modelling with its clarification question response?

As detailed in Table 1 of the company submission, tocilizumab is not considered a relevant comparator for this appraisal, due to its limited use as a treatment option for GCA patients.

The NICE recommendation for tocilizumab specifies use in relapsed/refractory patients only, with a restricted maximum one-year treatment duration.¹ The fixed one-year treatment duration represents a significant constraint, as patients frequently experience high relapse rates following treatment cessation. Critically, tocilizumab is not recommended for patients who have previously received the treatment, meaning patients cannot be re-treated upon relapse after one year, and patients are forced to return to corticosteroid therapy.

As such, tocilizumab is considered a short-term treatment for a limited number of patients and is often further reserved for those with an increased risk of corticosteroid related adverse events (AEs). Clinical experts consulted at an advisory board (Appendix B14) and consultees responding to the NICE scope are very clear that GCA is a chronic condition that often requires repeated, long-term treatment of corticosteroids over a patient's lifetime.² Upadacitinib is indicated as a treatment options for GCA in adult patients, with the flexibility to treat patients long term if required. In this broad population, corticosteroids remain the established standard of care and as such represent the relevant comparator for upadacitinib.

Furthermore, clinical experts have consistently highlighted the limited use of tocilizumab in real-world clinical practice. This limited use is driven by the optimised NICE recommendation and significant administrative challenges associated with prescribing the treatment, meaning few GCA patients are treated with tocilizumab in

clinical practice. The barriers and delays mean clinicians rely on corticosteroid treatment to rapidly manage relapses (Appendix B14). These challenges are also echoed in a recent report by the Getting It Right First Time (GIRFT) NHS programme³ which reported the use of tocilizumab is lower than anticipated due to the additional bureaucracy associated with access.

The limited use of tocilizumab in GCA patients is confirmed in UK market share data. Among a sample of ■ GCA patients in 2023/24, only ■ received tocilizumab treatment.⁴ This low utilisation rate of approximately ■ has persisted since tocilizumab's introduction for GCA in 2018,⁵ highlighting the limited use of tocilizumab in clinical practice.

While an ITC comparing upadacitinib and tocilizumab is not considered relevant, it would also yield substantial uncertainty due to heterogeneity between the SELECT-GCA and GiACTA trials,^{6,7} thus limiting the validity and clinical value of such a comparison.

In summary, given the fundamental differences in treatment positioning and anticipated use, the limited real-world utilisation and the inherent treatment restrictions that ultimately return patients to corticosteroid therapy, tocilizumab is not considered a relevant comparator for this appraisal. Corticosteroids are considered the appropriate comparator, reflecting established standard of care and evidenced through market data.

A2. Please provide the number of UK patients randomised in the SELECT - GCA in each of the treatment arms in the trial.

The number of UK patients randomised in the SELECT-GCA trial was ■, with ■ in the PBO + 52 WK CS-T arm and ■ in the UPA + 26 WK CS-T arm (■ in the 7.5 + 26 WK CS-T arm and ■ in the 15 + 26WK CS-T arm).⁸ The baseline characteristics across the upadacitinib and placebo arms were generally balanced and were representative of the UK population. Most patients were from Western Europe (55.4%) and white (92.0%), which make the results generalisable to a UK population.^{6,9} Expert opinion from clinicians in the UK agreed that the trial demographics were reflective of a UK population.

A3. There may be some ambiguity in the draft SmPC about whether

[REDACTED]
[REDACTED]
[REDACTED] ? What proportion of flares during SELECT-GCA Period 1 were acute relapses in the upadacitinib 15mg arm and the placebo arm?

The term 'acute relapse' is used in the SmPC to denote any type of disease flare and does not distinguish between relapse severity. Therefore, an acute relapse refers to the recurrence of disease signs and symptoms that necessitate an adjustment of treatment. Upadacitinib is licensed as a treatment for GCA in adult patients and should be used initially in combination with a tapering course of corticosteroids. Once the patient is in remission, and the patient has been successfully tapered off corticosteroids, patients may continue to use upadacitinib as a monotherapy beyond 52 weeks. The wording in section 4.2 and 4.4 of the SmPC is very clear that upadacitinib as a monotherapy should not be used to treat acute relapse.

Aligned with this, Section 4.4 of the tocilizumab SmPC also includes an analogous recommendation that 'monotherapy should not be used for the treatment of acute relapses as efficacy in this setting has not been established'.¹⁰ Therefore, this wording in the SmPC is well-understood by the clinical community, and AbbVie have been informed by clinical experts that it does not require further clarification. The number of disease flares is presented in company submission Section 2.6.1.2.

A4. Please provide CONSORT diagrams for SELECT-GCA covering the 35-day run in, Period 1 and Period 2, separately for ITT, new onset and relapsed (3 diagrams).

Separate CONSORT diagrams for the ITT, new onset, and relapsed populations are provided in Figure 1, Figure 2, and Figure 3.

Figure 1. SELECT-GCA ITT population CONSORT diagram

I

Figure 2. SELECT-GCA new onset population CONSORT diagram

I

Figure 3. SELECT-GCA relapsed population CONSORT diagram

I

A5. Please provide the ICD10 codes used to define the adverse events of Company Submission Tables 13, 14, 15, 17 and 18. Please also provide a list of the ICD10 codes that were used in defining adverse events possibly linked to steroid use during SELECT-GCA whether reported in Table 15 or not.

In SELECT-GCA, all adverse events were collected and reported using primary Medical Dictionary for Regulatory Affairs (MedDRA) System Organ Classes (SOC) and preferred terms (PT) according to MedDRA 26.1 coding dictionary.¹¹ The reliability of mapping between MedDRA and ICD-10 is considered moderate and presents a complex challenge due to their differing purposes and levels of detail.¹² MedDRA is a more granular reporting and is purposefully designed for regulatory reporting and pharmacovigilance.¹¹ In contrast, ICD-10 is a broader classification system often used for epidemiology statistics or insurance purposes, providing more general diagnostic categories.¹³ Due to the differences in structure, purpose and granularity, and the requirement of a clinician with in-depth knowledge, AbbVie is unable to map the adverse events observed in SELECT-GCA to ICD10 codes.

A6. What proportions of the ITT, new onset and relapsed were ICD10 M31.6 and what proportions were ICD10 M31.5?

As stated above, SELECT-GCA utilised MedDRA 26.1 for coding medical data including adverse events and medical history. As such, AbbVie are unable to provide this data. However, data was collected on the proportion of patients with a history of polymyalgia rheumatica at baseline. As ICD10 M31.5 corresponds to GCA with polymyalgia rheumatica and ICD10 M31.6 corresponds to 'other GCA', data on history of PMR at baseline are detailed in Table 1.

Table 1. SELECT-GCA: history of unequivocal symptoms of PMR at baseline

Treatment arm		History of unequivocal symptoms of PMR, n (%)
ITT	Placebo + 52 WK CS-T (n = 112)	69 (61.6%)
	UPA + 26 WK CS-T (n = 209)	109 (52.2%)
New onset	Placebo + 52 WK CS-T (n = ■)	■
	UPA + 26 WK CS-T (n = ■)	■
Relapsed	Placebo + 52 WK CS-T (n = ■)	■
	UPA + 26 WK CS-T (n = ■)	■

Abbreviations: CS-T: corticosteroid taper; ITT: intention-to-treat; PMR: polymyalgia rheumatica; UPA: upadacitinib; WK: week

A7. For age please provide the SELECT-GCA baseline characteristic sample size N, mean, min, lower quartile, upper quartile, max, sample standard deviation and standard error of the mean separately for the ITT population, the newly diagnosed subgroup and the relapsed subgroup separately for the upadacitinib arm and the placebo arm. Please present this for all patients, female patients and male patients (3 tables).

Please find below the age summary tables separately for the ITT population (Table 2) and newly diagnosed (Table 3) and relapsed subgroups (Table 4). The ages across the patient populations and treatment groups are consistent and expert opinion from clinicians agreed that ages in the overall population in SELECT-GCA are reflective of a UK GCA population.

Table 2. SELECT-GCA: summary of age, ITT population

	PBO + 52 WK CS-T	UPA + 26 WK CS-T
Overall		
N	112	209
Mean (SD)	71.6 (7.33)	70.8 (7.31)
Median	████	████
Q1, Q3	██████	██████
Min, Max	████	████
SEM	████	████
Male		
N	35	53
Mean (SD)	██████	██████
Median	████	████
Q1, Q3	██████	██████
Min, Max	████	████
SEM	████	████
Female		
N	77	156
Mean (SD)	██████	██████
Median	████	████
Q1, Q3	██████	██████
Min, Max	████	████
SEM	████	████

Abbreviations: CS-T: corticosteroid taper; N: number of observations; PBO: placebo; Q1: first quartile; Q3: third quartile; SD: standard deviation; SEM: standard error of the mean; UPA: upadacitinib; WK: week

Table 3. SELECT-GCA: summary of age, new onset population

	PBO + 52 WK CS-T	UPA + 26 WK CS-T
Overall		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
SEM		
Male		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
SEM		
Female		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		

Abbreviations: CS-T: corticosteroid taper; N: number of observations; PBO: placebo; Q1: first quartile; Q3: third quartile; SD: standard deviation; SEM: standard error of the mean; UPA: upadacitinib; WK: week

Table 4. SELECT-GCA: summary of age, relapsed population

	PBO + 52 WK CS-T	UPA + 26 WK CS-T
Overall		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
SEM		
Male		
N		
Mean (SD)		
Median		
Q1, Q3		

Min, Max	████	████
SEM	██	██
Female		
N	█	█
Mean (SD)	████	████
Median	██	██
Q1, Q3	████	████
Min, Max	████	████
SEM	██	██

Abbreviations: CS-T: corticosteroid taper; N: number of observations; PBO: placebo; Q1: first quartile; Q3: third quartile; SD: standard deviation; SEM: standard error of the mean; UPA: upadacitinib; WK: week

A8. Priority question. For the start of Period 1, i.e. after the 35-day run in period, please present the numbers of patients with the complications listed in table 31 and in table 32 separately for the ITT, new onset and relapsed, using the same ICD10 codes as reference 44 for the complications of table 31. If it is also possible to split the numbers with psychiatric disorders into the lowest level of ICD10 codes this would be much appreciated. Please also present this for the end of Period 1.

As described in responses A5 and A6, the MedDRA 26.1 classification system was utilised to define adverse events in the SELECT-GCA study. AbbVie is unable to map the adverse events observed in SELECT-GCA to ICD10 codes. Appendix A8 presents the adverse events observed in SELECT-GCA, categorised by System Organ Class and Preferred Term.

As emphasised in the company submission, the overall adverse event rates and corticosteroid-related adverse events in SELECT-GCA, along with those from other randomised controlled trials, do not fully capture the long-term risks associated with corticosteroid exposure. This limitation is due to the controlled trial environment, the relatively short follow-up period of 52 weeks, and the chronic nature of many corticosteroid-related adverse events.

To address this, real-world evidence (RWE) was incorporated to inform economic modelling for corticosteroid-related complications, providing a more comprehensive and representative account of the cumulative and variable risks associated with long-term corticosteroid use. This approach aligns with clinical feedback and the methodology used for deriving corticosteroid-related adverse events, as accepted in

TA518.¹ However, in TA518, the committee acknowledged that the model did not include an exhaustive list of adverse events resulting from long-term corticosteroid use, identifying this as a limitation. The RWE study addressed this by capturing a comprehensive list of adverse events, offering the most robust approach to estimating the negative impact of corticosteroids on costs and quality of life.

Randomised controlled trials do not fully capture all corticosteroid-related adverse events. Adverse events in the placebo group of SELECT-GCA (average of ■ mg daily) reported over 52 weeks are compared with a daily threshold range in the RWE study (■ mg daily) are shown in Table 5, with additional comparisons to UK literature where available.¹⁴⁻¹⁶ Key reported adverse events were higher in the RWE study, with increased rates of diabetes, stroke, atherosclerosis, osteoporosis, gastritis, psychiatric events, and cataracts, while weight gain and hypertension were notable adverse events which were higher in the SELECT-GCA placebo group.

These data suggest that the real-world incidence of corticosteroid adverse events is higher than what has been observed in randomised clinical trials such as SELECT-GCA. The event rates observed in this RWE study, and its inclusion for the purpose of corticosteroid AE modelling in this submission, was validated with UK clinicians who agreed that the RWE study AE rates were more representative of what is observed in UK clinical practice.

Table 5. Comparison of AEs across MarketScan RWE study, the SELECT-GCA trial, and relevant UK literature

MarketScan RWE Study (over 12 months of exposure time for oral corticosteroids cohort)		SELECT-GCA Trial (SS1) PBO – 52 WEEK CS-T		Literature summary (52-week data)	
Cumulative corticosteroid range: > ██████████ mg Daily average dose: 5-10mg		Median cumulative corticosteroid: 2882 mg Daily average dose: 7.8mg		Cumulative corticosteroid range: > 960.0 to ≤ 3054.9 mg Daily average dose: 2.6mg-8.4mg	Source
	██████		██████		
Any adverse event	██████	Any adverse event	██████		
Metabolic events	██████	Metabolism and nutrition disorders			
Increased BMI	██████	Weight increase	██████		
Newly diagnosed pre-diabetes	██████	Steroid diabetes	██████		
Newly diagnosed or treated for type 2 diabetes	██████	Type 2 diabetes mellitus	██████	3.2%	Wu et al., 2020 ¹⁶
Newly diagnosed or treated for hyperlipidaemia	██████	Hyperlipidaemia	██████		
Newly diagnosed endocrine adrenal insufficiency	██████	Adrenal suppression	██████		
Newly diagnosed or treated Cushing's syndrome	██████	Cushing's syndrome	██████		
Cardiovascular events	██████	Cardiac disorders		6.2%	Pujades-Rodriguez et al., 2020 ¹⁴
Newly diagnosed or treated hypertension	██████	Hypertension	██████		
Newly diagnosed electrolytes (sodium, potassium) abnormalities	██████	Blood sodium/potassium decreased	██████		
Hospitalization with myocardial infarction	██████	Non-fatal MI	██████	0.8%	Pujades-Rodriguez et al., 2020 ¹⁴
Hospitalization with stroke	██████	Non-fatal stroke	██████	1.0%	Pujades-Rodriguez et al., 2020 ¹⁴
Hospitalization with heart failure	██████	Cardiac failure	██████	1.6%	Pujades-Rodriguez et al., 2020 ¹⁴

Newly diagnosed or treated for atherosclerosis	■	Arteriosclerosis coronary artery	■		
Newly diagnosed palpitations	■	Palpitations	■		
Bone density events	■	Musculoskeletal and connective tissue disorders			
Newly diagnosed or treated for osteoporosis	■	Osteoporosis	■		
Newly diagnosed non-traumatic fracture	■	All fractures	■		
Musculoskeletal events	■		■		
Newly diagnosed myopathy	■	Myopathy	■		
Newly diagnosed aseptic necrosis of bone	■		■		
Newly diagnosed tendon rupture	■	Tendon disorder	■		
Newly diagnosed osteonecrosis	■		■		
Gastrointestinal (GI) events	■	Gastrointestinal disorders			
Newly diagnosed GI perforation	■	GI perforation	■		
Newly diagnosed for ulcer/GI bleed	■	Ulcers	■		
Newly diagnosed gastritis	■	Gastritis	■		
Psychiatric events	■	Psychiatric disorders			
Newly diagnosed or treated anxiety, depression, mania, hyperactivity, psychosis, or delirium	■	Pooled anxiety, depression, mania, psychosis and delirium	■		
Any Infection events	■	Infections and infestations		42.9%	Wu et al., 2019 ¹⁵
Newly Diagnosed Opportunistic infections**	■		■		
Newly diagnosed pneumonia	■	Pneumonia	■		
Newly diagnosed herpes zoster	■	Herpes zoster		2.7%	
Newly diagnosed candidiasis	■	Oral candida	■		
Newly diagnosed Tuberculosis	■	Latent TB	■		
Newly diagnosed sepsis	■	Sepsis	■		
Severe infection: Hospitalizations	■	Serious infections		10.7%	

Ocular events	■	Eye disorders			
Newly diagnosed cataract (Traumatic and congenital cataracts were excluded)	■	Cataract	■		
Newly diagnosed or treated glaucoma	■	Glaucoma	■		
Newly diagnosed increased IOP	■	IOP increased	■		
Sleep disorders	■		■		
Newly diagnosed or treated sleep disorders	■	Sleep disorders	■		
Newly diagnosed dyspnoea	■	Dyspnoea	■		
Skin events	■	Skin and subcutaneous tissue disorders			
Newly diagnosed bruising	■	Increased tendency to bruise	■		
Newly diagnosed skin thinning	■		■		
Newly diagnosed impaired wound healing	■		■		
Newly diagnosed acne	■	Acne	■		
Additional events	■		■		
Newly diagnosed hirsutism	■	Hirsutism	■		

**Opportunistic infections included pneumonia, herpes zoster, candidiasis, tuberculosis, aspergillosis, cryptococcosis, pneumocystis, cytomegalovirus, salmonella, mycobacteria (non-TB), toxoplasmosis, coccidiomycosis, histoplasmosis

Abbreviations: CS-T, corticosteroid taper; PBO, placebo; SS1: safety analysis set in Period 1; WK, week

In the company submission, Figure 7 shows time to first flare (FAS1), from when subjects first meet all three criteria in one assessment: absence of recurrence of GCA signs and symptoms, normalisation of ESR, and no corticosteroid dose increase. A subject not meeting the criteria for disease flare is considered having a disease flare at baseline.

In the SELECT-GCA trial a disease flare was not considered an inverse of remission because in addition to presence of GCA signs and symptoms and non-adherence to protocol defined CS taper patients also had to have an increase in corticosteroid dose. Therefore, the number of patients who were not in remission (shown in the SELECT-GCA CSR Figures 14.2_26.1 and 14.2_26.2) do not correspond with time to first flare shown in the company submission Figure 7, as there were patients in the trial who were neither in remission nor flare state as they did not meet the criteria for remission but also did not need an increase in corticosteroid dose.

In line with TA518, it would not be appropriate to populate the model with patient data from the SELECT-GCA trial who did not meet the criteria for disease flare (absence of recurrence of GCA signs and symptoms, normalisation of ESR, and no corticosteroid dose increase) when entering the trial. Therefore, any patients who did not meet the criteria for flare (based on three criteria) upon entering the SELECT-GCA trial were censored for the economic model.¹ During the TA518 submission, it was noted that eligibility criteria in GiACTA similarly included patients who were not in remission at baseline. As a result, the economic model submitted initially included patients who were not in remission at baseline. The committee expressed concern that this might bias the primary endpoint of the trial in favour of tocilizumab because it is less likely that people whose disease had not responded to high-dose corticosteroids would achieve remission with the lower tapering doses.¹ Therefore, the company submission followed the committee's preferred approach by censoring patients who were not in remission at baseline for the economic model. This approach can be considered conservative using the rationale provided during TA518 and aligns with the model structure presented in Section 3.2.2 of the company submission, which requires patients to start in a pre-flare remission health state.

Proportion of Subjects in Remission by Visit through Week 52

Please find the tabulated data for SELECT-GCA CSR Figures 14.2_26.1 and 14.2_26.2 in Table 6 and Table 7.

Table 6. SELECT-GCA: Proportion of Subjects in Remission at Each Visit through Week 52 by subgroup (NRI-MI)

	PBO + 52 WK CS-T			UPA + 26 WK CS-T		
ITT population	N	n (%)	95% CI	N	n (%)	95% CI
Baseline	112			209		
Week 2	112			209		
Week 4	112			209		
Week 8	112			209		
Week 12	112			209		
Week 16	112			209		
Week 20	112			209		
Week 24	112			209		
Week 28	112			209		
Week 36	112			209		
Week 44	112			209		
Week 52	112			209		
New onset subgroup	N	n (%)	95% CI	N	n (%)	95% CI
Baseline	76			148		
Week 2	76			148		
Week 4	76			148		
Week 8	76			148		
Week 12	76			148		
Week 16	76			148		
Week 20	76			148		
Week 24	76			148		
Week 28	76			148		
Week 36	76			148		
Week 44	76			148		
Week 52	76			148		
Relapsed subgroup	N	n (%)	95% CI	N	n (%)	95% CI
Baseline	36			61		
Week 2	36			61		
Week 4	36			61		
Week 8	36			61		
Week 12	36			61		
Week 16	36			61		

Week 20	36			61		
Week 24	36			61		
Week 28	36			61		
Week 36	36			61		
Week 44	36			61		
Week 52	36			61		

Abbreviations: CI: confidence interval; CS-T: corticosteroid taper; ITT: intention-to-treat; N: number in population; n: number of observations; PBO: placebo; UPA: upadacitinib; WK: week

Table 7. SELECT-GCA: proportion of Subjects in Remission at Each Visit through Week 52 by subgroup (AO)

	PBO + 52 WK CS-T			UPA + 26 WK CS-T		
ITT population	N	n (%)	95% CI	N	n (%)	95% CI
Baseline	112			209		
Week 2	111			208		
Week 4	110			206		
Week 8	105			200		
Week 12	103			195		
Week 16	102			196		
Week 20	100			192		
Week 24	99			190		
Week 28	99			185		
Week 36	97			187		
Week 44	95			186		
Week 52	91			182		
New onset subgroup	N	n (%)	95% CI	N	n (%)	95% CI
Baseline	76			148		
Week 2	76			148		
Week 4	74			146		
Week 8	72			140		
Week 12	71			139		
Week 16	70			139		
Week 20	68			135		
Week 24	67			134		
Week 28	67			133		
Week 36	67			132		
Week 44	65			131		
Week 52	61			129		
Relapsed subgroup	N	n (%)	95% CI	N	n (%)	95% CI
Baseline	36			61		

Week 2	35			60		
Week 4	36			60		
Week 8	33			60		
Week 12	32			56		
Week 16	32			57		
Week 20	32			57		
Week 24	32			56		
Week 28	32			52		
Week 36	30			55		
Week 44	30			55		
Week 52	30			53		

Abbreviations: CI: confidence interval; CS-T: corticosteroid taper; ITT: intention-to-treat; N: number in population; n: number of observations; PBO: placebo; UPA: upadacitinib; WK: week

A10. Section 2.3.1.1 states that SELECT-GCA was double blind. How is this maintained given that the open label GC tapering schedules for doses above 20mg differ between the arms. Please also confirm whether those not in remission at Period 1 baseline followed the tapering schedule from Period 1 baseline or tapered at a later date once remission had been achieved.

During the SELECT-GCA trial Period 1, the initial corticosteroid dose of 20 mg, 30 mg, 40 mg, 50 mg, or 60 mg was determined at the discretion of the investigator, based on disease severity and confounding medical conditions (i.e., not impacted by treatment arm). Open-label corticosteroids were provided following the protocol defined tapering schedule until patients reached a 20 mg of prednisolone dose per day. Subsequently, blinded corticosteroids were provided for the remaining blinded taper regimen, as the tapering schedule diverges between the 26-week and 52-week taper as shown in Table 8. The double blind integrity of the trial was maintained as this tapering schedule was identical across placebo and upadacitinib arms, ensuring investigators could not differentiate treatment allocation based on steroid tapering patterns alone.⁹

Regarding the second part of the question, as outlined in response to A9, patients who were not in remission also followed the same tapering schedule as it was not an inclusion criterion for the trial.

Table 8. SELECT-GCA: corticosteroid tapering schedule⁹

Week	Blinded 52-week CS taper (dose in mg)					Blinded 26-week CS taper (dose in mg)				
Baseline	20	30	40	50	60	20	30	40	50	60
1	17	25	35	40	50	15	25	35	40	50
2	17	20	30	35	40	12	20	30	35	40
3	15	17	25	30	35	12	15	25	30	35
4	15	17	20	25	30	10	12	20	25	30
5	12	15	17	20	25	9	12	15	20	25
6	10	15	17	17	20	8	10	12	15	20
7	10	12	15	17	17	7	9	12	12	15
8	10	10	15	15	17	6	8	10	12	12
9	10	10	12	15	15	6	7	9	10	12
10	9	10	10	12	15	5	6	8	9	10
11	9	10	10	10	12	5	6	7	8	9
12	9	9	10	10	10	4	5	6	7	8
13	9	9	10	10	10	4	5	6	6	7
14	8	9	9	10	10	3	4	5	6	6
15	8	9	9	9	10	3	4	5	5	6
16	8	8	9	9	9	2	3	4	5	5
17	8	8	9	9	9	2	3	4	4	5
18	7	8	8	9	9	1	2	3	4	4
19	7	8	8	8	9	1	2	3	3	4
20	7	7	8	8	8	0	1	2	3	3
21	7	7	8	8	8	0	1	2	2	3
22	6	7	7	8	8	0	0	1	2	2
23	6	7	7	7	8	0	0	1	1	2
24	6	6	7	7	7	0	0	0	1	1
25	6	6	7	7	7	0	0	0	0	1
26	5	6	6	7	7	0	0	0	0	0
27	5	6	6	6	7	0	0	0	0	0
28	5	5	6	6	6	0	0	0	0	0
29	5	5	6	6	6	0	0	0	0	0
30	4	5	5	6	6	0	0	0	0	0
31	4	5	5	5	6	0	0	0	0	0
32	4	4	5	5	5	0	0	0	0	0
33	4	4	5	5	5	0	0	0	0	0
34	3	4	4	5	5	0	0	0	0	0
35	3	4	4	4	5	0	0	0	0	0
36	3	3	4	4	4	0	0	0	0	0
37	3	3	4	4	4	0	0	0	0	0
38	2	3	3	4	4	0	0	0	0	0
39	2	3	3	3	4	0	0	0	0	0
40	2	2	3	3	3	0	0	0	0	0
41	2	2	3	3	3	0	0	0	0	0
42	1	2	2	3	3	0	0	0	0	0
43	1	2	2	2	3	0	0	0	0	0
44	1	1	2	2	2	0	0	0	0	0
45	1	1	2	2	2	0	0	0	0	0
46	0	1	1	2	2	0	0	0	0	0
47	0	1	1	1	2	0	0	0	0	0
48	0	0	1	1	1	0	0	0	0	0
49	0	0	1	1	1	0	0	0	0	0
50	0	0	0	1	1	0	0	0	0	0
51	0	0	0	0	1	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0

Note: Grey cells indicate open-label corticosteroid doses

A11. Please present the distribution of mean daily steroid dose during Period 1 separately by arm separately for the ITT, new onset and relapsed using (1) the cutoffs of reference 44 and (2) the cutoffs of Raw_Safety cells C263:R314. Please do not weight this by patient duration of steroid treatment; i.e. mean dose = cohort total mg / total patient days in Period 1 whether on steroids or not.

Mean daily corticosteroid dose was calculated as the total cumulative corticosteroid dose during Period 1, divided by the total days in study during Period 1. Mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum were reported for continuous variable – mean daily CS Dose (Table 9). Frequency and percentage were calculated for mean daily CS dose categories for cutoffs of reference 44 and (2) the cutoffs of Raw_Safety cells C263:R314 (Table 10).

Table 9. SELECT-GCA: daily corticosteroid dose during Period 1

	PBO + 52 WK CS-T	UPA + 26 WK CS-T
ITT population		
N	112	209
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
New onset subgroup		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Relapsed subgroup		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		

Abbreviations: CS-T: corticosteroid taper; ITT: intention-to-treat; N: number of observations; PBO: placebo; Q1: first quartile; Q3: third quartile; SD: standard deviation; UPA: upadacitinib; WK: week

Table 10. SELECT-GCA: frequency and percentage for mean daily corticosteroid dose categories during Period 1

	PBO + 52 WK CS-T n (%)	UPA + 26 WK CS-T n (%)
ITT population		
Mean daily corticosteroid dose category 1 (cutoffs of reference 44)		
Low dose: > 0 to ≤ 7.5 mg		
Medium dose: > 7.5 to ≤ 20 mg		
High dose: > 20 to ≤ 40 mg		
Very high dose: > 40 mg		
Mean daily corticosteroid dose category 2 (cutoffs of Raw_Safety cells C263:R314)		
Low dose: ≤ 5 mg		
Medium dose: > 5 to ≤ 10 mg		
High dose: > 10 to ≤ 20 mg		
Very high dose: > 20 to ≤ 40 mg		
Extremely high dose: > 40 mg		
New onset subgroup		
Mean daily corticosteroid dose category 1 (cutoffs of reference 44)		
Low dose: > 0 to ≤ 7.5 mg		
Medium dose: > 7.5 to ≤ 20 mg		
High dose: > 20 to ≤ 40 mg		
Very high dose: > 40 mg		
Mean daily corticosteroid dose category 2 (cutoffs of Raw_Safety cells C263:R314)		
Low dose: ≤ 5 mg		
Medium dose: > 5 to ≤ 10 mg		
High dose: > 10 to ≤ 20 mg		
Very high dose: > 20 to ≤ 40 mg		
Extremely high dose: > 40 mg		
Relapsed subgroup		
Mean daily corticosteroid dose category 1 (cutoffs of reference 44)		
Low dose: > 0 to ≤ 7.5 mg		
Medium dose: > 7.5 to ≤ 20 mg		
High dose: > 20 to ≤ 40 mg		
Very high dose: > 40 mg		
Mean daily corticosteroid dose category 2 (cutoffs of Raw_Safety cells C263:R314)		
Low dose: ≤ 5 mg		
Medium dose: > 5 to ≤ 10 mg		
High dose: > 10 to ≤ 20 mg		
Very high dose: > 20 to ≤ 40 mg		
Extremely high dose: > 40 mg		

Abbreviations: CS-T: corticosteroid taper; ITT: intention-to-treat; N: number of observations; PBO: placebo; Q1: first quartile; Q3: third quartile; SD: standard deviation; UPA: upadacitinib; WK: week

A12. Please present the total mean steroid dose separately for (1) the 35 day run in period and (2) Period 1, separately for those who were randomized to upadacitinib 15mg and to placebo, separately for the ITT, the new onset and the relapsed (12 values).

Mean daily corticosteroid dose was calculated as the total cumulative corticosteroid dose during Period 1, divided by the total days in study during Period 1. Mean, standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum were reported for continuous variable – mean daily CS Dose. The cumulative corticosteroid dose for the 35-day Screening Period and Period 1 are presented in Table 11 and Table 12, respectively.

Table 11. SELECT-GCA cumulative corticosteroid dose during the 35-day Screening Period

	PBO + 52 WK CS-T	UPA + 26 WK CS-T
ITT population		
N	112	209
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
New onset subgroup		
N		
Mean (SD)		
Median		
Min, Max		
Relapsed subgroup		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		

Abbreviations: CS-T: corticosteroid taper; N: number of observations; PBO: placebo; SD: standard deviation; UPA: upadacitinib; WK: week

Table 12. SELECT-GCA total corticosteroid dose during Period 1

	PBO + 52 WK CS-T	UPA + 26 WK CS-T

ITT population		
N		
Mean (SD)		
Median	2882.0	1615.0
Q1, Q3		
Min, Max		
New onset subgroup		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Relapsed subgroup		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		

Abbreviations: CS-T: corticosteroid taper; N: number of observations; PBO: placebo; SD: standard deviation; UPA: upadacitinib; WK: week

A13. For Table 51 of the Appendices please augment the estimates of mean disease duration since diagnoses (days) with the mean cumulative steroid administered during these disease durations.

AbbVie are unable to provide this analysis as data on cumulative steroids received was not collected prior to baseline for any patients.

A14. Company clinical experts indicate that 20% of flares will be “severe flares”. The SmPC mentions “acute relapses” What is the definition of “acute flares” and how much do they correspond with “severe flares”. What was the protocol during SELECT-GCA with regards “acute relapses” in terms of upadacitinib use and other treatments and/or interventions? Given the SmPC, if patients are receiving upadacitinib and experience an “acute relapse” should they in practice have upadacitinib treatment withdrawn? Likewise, should patients not receiving upadacitinib who have an “acute relapse” be treated with upadacitinib with a tapering course of steroids? Is the 40mg GC dose for

acute relapse solely based upon company expert opinion or is this dose recommended elsewhere; e.g. by the BSR?

As outlined in question A3, the term 'acute relapse' does not distinguish between relapse severity but rather refers to the sudden recurrence of disease signs and symptoms that requires an adjustment of treatment. This is in line with the definition of a flare in the SELECT-GCA trial and so all flares are assumed to be acute relapses. As per the trial protocol all disease flares were treated with open-label escape therapy using prednisolone and remaining on upadacitinib or placebo for the full 52 weeks. After 2 weeks of corticosteroid escape therapy, if deemed medically necessary to treat with other treatments, upadacitinib or placebo and corticosteroid could be discontinued. Therefore, in practice if a patient receiving upadacitinib experiences an 'acute relapse', corticosteroid adjustment can be made depending on relapse severity without withdrawing upadacitinib therapy. Likewise, patients not being treated with upadacitinib who have an 'acute relapse' can be treated with upadacitinib along with a tapering course of corticosteroids as upadacitinib is licensed for the treatment of all adult patients with GCA in combination with a tapering course of corticosteroids. Relapse, or flare severity is classified in the EULAR guidelines as either minor or major, depending on symptom severity along with management guidance for corticosteroid dose increase. Major relapse (severe flare) is defined as the recurrence of active disease with either; clinical features of ischemia, or evidence of active aortic inflammation, and is treated with a dose escalation between 40–60 mg of corticosteroids. A minor relapse is defined as the recurrence of active disease, not fulfilling the criteria of a major relapse, and is recommended to be treated by returning to the last effective corticosteroid dose.

Aligned with this guidance, the economic model applied a conservative dose escalation to 40 mg corticosteroid for the 20% of flares considered as severe flares. Minor flares were modelled by reverting to the last effective dose, determined by the daily corticosteroid dose in the previous cycle while in pre-flare remission state. A dose escalation to 60 mg for the treatment of severe flares was also explored as a scenario analysis for completeness.

A15. Priority question. Please provide the Kaplan Meier data:

- 1) Separately for upadacitinib 15mg and for placebo that underlies Figure 7 and its equivalent for the new onset subgroup and for the relapsed subgroup (6 Tables). Please also provide this for Figure 14 and its equivalent for the new onset subgroup and for the relapsed subgroup (6 Tables). Please provide an account of the differences between Figure 7 and Figure 14.**

The SELECT-GCA trial defined time to first flare as the time in days from when the patient is in remission (absence of recurrence of GCA signs and symptoms; normalisation of ESR; and no CS dose increase), until the occurrence of the first protocol defined disease flare. In the company submission Figure 7, if a patient never meets all three criteria in one assessment during Period 1 (i.e., is not in remission), the patient is considered as having a disease flare at baseline. In company submission Figure 14, if a patient did not meet all three criteria at baseline during Period 1, the patient is censored at baseline. Further detail on the differences between the analysed population in the company submission Figure 7 and Figure 14 is provided in response to question B1.

As stated in response to question A9, censoring these patients in the economic model follows the approach taken during TA518¹.

The requested tables are provided below:

- Time to first flare as defined in SELECT-GCA (company submission Figure 7):
 - FAS1 population:
 - Table 13: placebo plus 52-week corticosteroid taper
 - Table 14: upadacitinib 15 mg plus 26-week corticosteroid taper
 - Patients with new onset disease:
 - Table 15: placebo plus 52-week corticosteroid taper
 - Table 16: upadacitinib 15 mg plus 26-week corticosteroid taper

- Patients with relapsed disease
 - Table 17: placebo plus 52-week corticosteroid taper
 - Table 18: upadacitinib 15 mg plus 26-week corticosteroid taper
- Time to first flare with patients who did not meet the flare criteria censored (company submission Figure 14):
 - FAS1 population:
 - Table 19: placebo plus 52-week corticosteroid taper
 - Table 20: upadacitinib 15 mg plus 26-week corticosteroid taper
 - Patients with new onset disease:
 - Table 21: placebo plus 52-week corticosteroid taper
 - Table 22: upadacitinib 15 mg plus 26-week corticosteroid taper
 - Patients with relapsed disease
 - Table 23: placebo plus 52-week corticosteroid taper
 - Table 24: upadacitinib 15 mg plus 26-week corticosteroid taper

Table 13. SELECT-GCA: time to first flare through Week 52 (FAS1) – placebo plus 52-week corticosteroid taper (all patients)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0	112	0	0	100.00%	100.00%	100.00%
0	112	9	0	91.96%	85.13%	95.74%
1	103	0	3	91.96%	85.13%	95.74%
8	100	1	0	91.04%	83.99%	95.08%
15	99	0	1	91.04%	83.99%	95.08%
29	98	1	0	90.12%	82.86%	94.40%
34	97	1	0	89.19%	81.74%	93.71%
34	96	0	1	89.19%	81.74%	93.71%
36	95	1	0	88.25%	80.62%	93.00%
37	94	1	0	87.31%	79.50%	92.28%
41	93	1	0	86.37%	78.40%	91.55%

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
43	92	6	0	80.74%	71.99%	87.00%
43	86	0	1	80.74%	71.99%	87.00%
44	85	1	0	79.79%	70.93%	86.20%
57	84	1	0	78.84%	69.88%	85.41%
70	83	1	0	77.89%	68.83%	84.60%
71	82	2	0	75.99%	66.76%	82.98%
74	80	0	1	75.99%	66.76%	82.98%
78	79	2	0	74.06%	64.67%	81.32%
91	77	0	1	74.06%	64.67%	81.32%
99	76	4	0	70.17%	60.50%	77.89%
113	72	1	0	69.19%	59.47%	77.03%
134	71	1	0	68.22%	58.45%	76.16%
140	70	1	0	67.24%	57.43%	75.28%
155	69	1	0	66.27%	56.41%	74.40%
159	68	1	0	65.29%	55.40%	73.51%
183	67	2	0	63.34%	53.39%	71.73%
197	65	0	1	63.34%	53.39%	71.73%
211	64	1	0	62.35%	52.38%	70.82%
225	63	1	0	61.36%	51.36%	69.91%
240	62	0	1	61.36%	51.36%	69.91%
248	61	1	0	60.36%	50.34%	68.98%
249	60	1	0	59.35%	49.31%	68.05%
283	59	0	2	59.35%	49.31%	68.05%
295	57	3	0	56.23%	46.14%	65.14%
296	54	1	0	55.19%	45.09%	64.17%
297	53	1	0	54.15%	44.05%	63.19%
304	52	1	0	53.11%	43.02%	62.20%
310	51	1	0	52.06%	41.99%	61.21%
310	50	0	1	52.06%	41.99%	61.21%
311	49	1	0	51.00%	40.93%	60.20%
323	48	1	0	49.94%	39.89%	59.18%
335	47	0	2	49.94%	39.89%	59.18%
337	45	0	1	49.94%	39.89%	59.18%
348	44	0	1	49.94%	39.89%	59.18%
349	43	0	2	49.94%	39.89%	59.18%
350	41	0	4	49.94%	39.89%	59.18%
351	37	0	28	49.94%	39.89%	59.18%
352	9	1	0	44.39%	30.79%	57.13%
352	8	0	3	44.39%	30.79%	57.13%
353	5	0	2	44.39%	30.79%	57.13%
356	3	0	1	44.39%	30.79%	57.13%
358	2	0	1	44.39%	30.79%	57.13%
365	1	0	1	44.39%	30.79%	57.13%

Abbreviations: CI, confidence interval.

Note: Time to first disease flare is calculated from when patients first meet all three criteria in one assessment: absence of recurrence of GCA signs and symptoms, normalisation of ESR, and no CS dose increase. If a patient never meets all three criteria in one assessment, the patient will be considered to have a disease flare at Day 0.

Table 14. SELECT-GCA: time to first flare through Week 52 (FAS1) – upadacitinib 15 mg plus 26-week corticosteroid taper (all patients)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0	209	0	0	100.00%	100.00%	100.00%
0	209	13	0	93.78%	89.53%	96.34%
1	196	0	1	93.78%	89.53%	96.34%
13	195	1	0	93.30%	88.95%	95.98%
15	194	1	0	92.82%	88.37%	95.61%
15	193	0	1	92.82%	88.37%	95.61%
23	192	1	0	92.33%	87.79%	95.23%
26	191	0	1	92.33%	87.79%	95.23%
41	190	1	0	91.85%	87.21%	94.85%
43	189	4	0	89.90%	84.94%	93.30%
44	185	1	0	89.42%	84.37%	92.90%
46	184	1	0	88.93%	83.81%	92.50%
48	183	1	0	88.45%	83.26%	92.10%
52	182	0	1	88.45%	83.26%	92.10%
53	181	0	1	88.45%	83.26%	92.10%
57	180	3	0	86.97%	81.58%	90.88%
57	177	0	1	86.97%	81.58%	90.88%
58	176	1	0	86.48%	81.02%	90.46%
71	175	1	0	85.98%	80.46%	90.04%
72	174	1	0	85.49%	79.90%	89.62%
72	173	0	1	85.49%	79.90%	89.62%
76	172	1	0	84.99%	79.35%	89.20%
85	171	0	1	84.99%	79.35%	89.20%
86	170	1	0	84.49%	78.79%	88.77%
88	169	0	1	84.49%	78.79%	88.77%
97	168	1	0	83.99%	78.22%	88.34%
99	167	3	0	82.48%	76.55%	87.04%
106	164	0	1	82.48%	76.55%	87.04%
113	163	1	0	81.98%	75.99%	86.60%
123	162	1	0	81.47%	75.43%	86.16%
126	161	1	0	80.96%	74.88%	85.72%
127	160	3	0	79.45%	73.22%	84.38%
127	157	0	1	79.45%	73.22%	84.38%
129	156	1	0	78.94%	72.66%	83.93%
129	155	0	1	78.94%	72.66%	83.93%
155	154	3	0	77.40%	71.00%	82.56%
155	151	0	1	77.40%	71.00%	82.56%
168	150	1	0	76.88%	70.44%	82.10%
175	149	1	0	76.37%	69.88%	81.64%
179	148	1	0	75.85%	69.33%	81.17%
182	147	1	0	75.33%	68.78%	80.71%
183	146	1	0	74.82%	68.22%	80.24%

186	145	0	1	74.82%	68.22%	80.24%
191	144	1	0	74.30%	67.67%	79.77%
192	143	1	0	73.78%	67.12%	79.30%
212	142	1	0	73.26%	66.56%	78.83%
219	141	1	0	72.74%	66.01%	78.36%
224	140	0	1	72.74%	66.01%	78.36%
225	139	1	0	72.22%	65.46%	77.88%
225	138	0	1	72.22%	65.46%	77.88%
232	137	0	1	72.22%	65.46%	77.88%
239	136	1	0	71.69%	64.89%	77.40%
240	135	1	0	71.15%	64.33%	76.91%
243	134	1	0	70.62%	63.77%	76.42%
246	133	1	0	70.09%	63.21%	75.94%
274	132	1	0	69.56%	62.65%	75.45%
283	131	0	1	69.56%	62.65%	75.45%
293	130	1	0	69.03%	62.09%	74.96%
295	129	0	1	69.03%	62.09%	74.96%
308	128	1	0	68.49%	61.52%	74.46%
308	127	0	1	68.49%	61.52%	74.46%
309	126	0	1	68.49%	61.52%	74.46%
330	125	0	1	68.49%	61.52%	74.46%
333	124	0	1	68.49%	61.52%	74.46%
336	123	0	3	68.49%	61.52%	74.46%
337	120	0	4	68.49%	61.52%	74.46%
338	116	0	1	68.49%	61.52%	74.46%
342	115	0	2	68.49%	61.52%	74.46%
344	113	0	1	68.49%	61.52%	74.46%
346	112	0	1	68.49%	61.52%	74.46%
347	111	0	1	68.49%	61.52%	74.46%
349	110	0	7	68.49%	61.52%	74.46%
350	103	1	0	67.82%	60.79%	73.87%
350	102	0	8	67.82%	60.79%	73.87%
351	94	0	62	67.82%	60.79%	73.87%
352	32	1	0	65.70%	57.58%	72.64%
352	31	0	14	65.70%	57.58%	72.64%
353	17	0	11	65.70%	57.58%	72.64%
355	6	0	2	65.70%	57.58%	72.64%
356	4	0	1	65.70%	57.58%	72.64%
360	3	0	1	65.70%	57.58%	72.64%
361	2	0	1	65.70%	57.58%	72.64%
363	1	0	1	65.70%	57.58%	72.64%

Abbreviations: CI, confidence interval.

Note: Time to first disease flare is calculated from when patients first meet all three criteria in one assessment: absence of recurrence of GCA signs and symptoms, normalisation of ESR, and no CS dose increase. If a patient never meets all three criteria in one assessment, the patient will be considered to have a disease flare at Day 0.

Table 15. SELECT-GCA: time to first flare through Week 52 (FAS1) – placebo plus 52-week corticosteroid taper (patients with new onset disease)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound

0									
0									
1									
8									
15									
34									
36									
37									
41									
43									
43									
44									
57									
70									
71									
74									
78									
91									
99									
113									
134									
140									
155									
159									
183									
197									
211									
225									
240									
249									
295									
296									
311									
323									
335									
348									
349									
350									
351									
352									
356									
358									

Abbreviations: CI, confidence interval

Note: Time to first disease flare is calculated from when patients first meet all three criteria in one assessment: absence of recurrence of GCA signs and symptoms, normalisation of ESR, and no CS dose increase. If a patient never meets all three criteria in one assessment, the patient will be considered to have a disease flare at Day 0.

Table 16. SELECT-GCA Time to first flare through Week 52 (FAS1) – upadacitinib 15 mg plus 26-week corticosteroid taper (patients with new onset disease)

Day	N at Risk	N event	N Censored	S(t)	95% CI

					Lower Bound	Upper Bound
0						
0						
1						
13						
15						
15						
23						
26						
41						
43						
44						
48						
52						
57						
57						
71						
72						
72						
76						
85						
86						
97						
99						
106						
123						
127						
127						
129						
129						
155						
175						
182						
186						
191						
212						
219						
224						
240						
243						
246						
274						
283						
295						
308						
308						
309						
330						
336						
337						
344						

346							
349							
350							
351							
352							
352							
353							
355							
356							
360							

Abbreviations: CI, confidence interval.

Note: Time to first disease flare is calculated from when patients first meet all three criteria in one assessment: absence of recurrence of GCA signs and symptoms, normalisation of ESR, and no CS dose increase. If a patient never meets all three criteria in one assessment, the patient will be considered to have a disease flare at Day 0.

Table 17. SELECT-GCA Time to first flare through Week 52 (FAS1) – placebo plus 52-week corticosteroid taper (patients with relapsed disease)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0						
0						
29						
34						
43						
71						
99						
183						
248						
283						
295						
297						
304						
310						
310						
335						
337						
349						
351						
352						
352						
353						
365						

Abbreviations: CI, confidence interval.

Note: Time to first disease flare is calculated from when patients first meet all three criteria in one assessment: absence of recurrence of GCA signs and symptoms, normalisation of ESR, and no CS dose increase. If a patient never meets all three criteria in one assessment, the patient will be considered to have a disease flare at Day 0.

Table 18. SELECT-GCA Time to first flare through Week 52 (FAS1) – upadacitinib 15 mg plus 26-week corticosteroid taper (patients with relapsed disease)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0	■	■	■	■	■	■
0	■	■	■	■	■	■
43	■	■	■	■	■	■
46	■	■	■	■	■	■
53	■	■	■	■	■	■
58	■	■	■	■	■	■
88	■	■	■	■	■	■
99	■	■	■	■	■	■
113	■	■	■	■	■	■
126	■	■	■	■	■	■
127	■	■	■	■	■	■
155	■	■	■	■	■	■
155	■	■	■	■	■	■
168	■	■	■	■	■	■
179	■	■	■	■	■	■
183	■	■	■	■	■	■
192	■	■	■	■	■	■
225	■	■	■	■	■	■
225	■	■	■	■	■	■
232	■	■	■	■	■	■
239	■	■	■	■	■	■
293	■	■	■	■	■	■
333	■	■	■	■	■	■
337	■	■	■	■	■	■
338	■	■	■	■	■	■
342	■	■	■	■	■	■
347	■	■	■	■	■	■
349	■	■	■	■	■	■
350	■	■	■	■	■	■
350	■	■	■	■	■	■
351	■	■	■	■	■	■
352	■	■	■	■	■	■
353	■	■	■	■	■	■
361	■	■	■	■	■	■
363	■	■	■	■	■	■

Abbreviations: CI, confidence interval.

Note: Time to first disease flare is calculated from when patients first meet all three criteria in one assessment: absence of recurrence of GCA signs and symptoms, normalisation of ESR, and no CS dose increase. If a patient never meets all three criteria in one assessment, the patient will be considered to have a disease flare at Day 0.

Table 19. SELECT-GCA: time to first flare through Week 52 with patients who did not meet the flare criteria censored (FAS1) – placebo plus 52-week corticosteroid taper (all patients)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0	■	■	■	■	■	■
8	■	■	■	■	■	■
29	■	■	■	■	■	■
34	■	■	■	■	■	■
36	■	■	■	■	■	■
37	■	■	■	■	■	■
41	■	■	■	■	■	■
43	■	■	■	■	■	■
44	■	■	■	■	■	■
57	■	■	■	■	■	■
70	■	■	■	■	■	■
71	■	■	■	■	■	■
78	■	■	■	■	■	■
99	■	■	■	■	■	■
113	■	■	■	■	■	■
134	■	■	■	■	■	■
140	■	■	■	■	■	■
155	■	■	■	■	■	■
159	■	■	■	■	■	■
183	■	■	■	■	■	■
211	■	■	■	■	■	■
225	■	■	■	■	■	■
248	■	■	■	■	■	■
249	■	■	■	■	■	■
295	■	■	■	■	■	■
296	■	■	■	■	■	■
297	■	■	■	■	■	■
304	■	■	■	■	■	■
310	■	■	■	■	■	■
311	■	■	■	■	■	■
323	■	■	■	■	■	■
352	■	■	■	■	■	■

Abbreviations: CI, confidence interval.

Table 20. SELECT-GCA: time to first flare through Week 52 with patients who did not meet the flare criteria censored (FAS1) – upadacitinib 15 mg plus 26-week corticosteroid taper (all patients)

Day	N at Risk	N event	N Censored	S(t)	95% CI

					Lower Bound	Upper Bound
0						
13						
15						
23						
41						
43						
44						
46						
48						
57						
58						
71						
72						
76						
86						
97						
99						
113						
123						
126						
127						
129						
155						
168						
175						
179						
182						
183						
191						
192						
212						
219						
225						
239						
240						
243						
246						
274						
293						
308						
350						
352						

Abbreviations: CI, confidence interval.

Table 21. SELECT-GCA: time to first flare through Week 52 with patients who did not meet the flare criteria censored (FAS1) – placebo plus 52-week corticosteroid taper (patients with new onset disease)

Day	N at Risk	N event	N Censored	S(t)	95% CI

					Lower Bound	Upper Bound
0						
8						
34						
36						
37						
41						
43						
44						
57						
70						
71						
78						
99						
113						
134						
140						
155						
159						
183						
211						
225						
249						
295						
296						
311						
323	33	32	1	0	54.09%	40.98%

Abbreviations: CI, confidence interval

Table 22. SELECT-GCA Time to first flare through Week 52 with patients who did not meet the flare criteria censored (FAS1) – upadacitinib 15 mg plus 26-week corticosteroid taper (patients with new onset disease)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0						
13						
15						
23						
41						
43						
44						
48						
57						
71						
72						
76						
86						
97						

99							
123							
127							
129							
155							
175							
182							
191							
212							
219							
240							
243							
246							
274							
308							
352							

Abbreviations: CI, confidence interval

Table 23. SELECT-GCA Time to first flare through Week 52 with patients who did not meet the flare criteria censored (FAS1) – placebo plus 52-week corticosteroid taper (patients with relapsed disease)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0						
29						
43						
71						
99						
183						
248						
295						
297						
304						
310						
352						

Abbreviations: CI, confidence interval

Table 24. SELECT-GCA Time to first flare through Week 52 with patients who did not meet the flare criteria censored (FAS1) – upadacitinib 15 mg plus 26-week corticosteroid taper (patients with relapsed disease)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0						
43						
46						

58									
99									
113									
126									
127									
155									
168									
179									
183									
192									
225									
239									
293									
350									

Abbreviations: CI, confidence interval

2) For Period 1 separately for upadacitinib 15mg and placebo for the time to subsequent flare taking the day of first flare as Day 0 separately for the ITT, the new onset subgroup and the relapsed subgroup (6 Tables).

The requested tables are provided below for time to subsequent flare:

- FAS1 population:
 - Table 25: placebo plus 52-week corticosteroid taper
 - Table 26: upadacitinib 15 mg plus 26-week corticosteroid taper
- Patients with new onset disease:
 - Table 27: placebo plus 52-week corticosteroid taper
 - Table 28: upadacitinib 15 mg plus 26-week corticosteroid taper
- Patients with relapsed disease
 - Table 29: placebo plus 52-week corticosteroid taper
 - Table 30: upadacitinib 15 mg plus 26-week corticosteroid taper

Table 25. SELECT-GCA: time to subsequent flare through Week 52 (FAS1) – placebo plus 52-week corticosteroid taper (all patients)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0	44	0	0	100.00%	100.00%	100.00%
0	44	8	0	81.82%	66.92%	90.46%
1	36	0	4	81.82%	66.92%	90.46%
11	32	1	0	79.26%	63.89%	88.64%
22	31	0	1	79.26%	63.89%	88.64%
31	30	0	1	79.26%	63.89%	88.64%
34	29	1	0	76.53%	60.65%	86.67%
41	28	0	1	76.53%	60.65%	86.67%
45	27	1	0	73.69%	57.36%	84.57%
58	26	0	2	73.69%	57.36%	84.57%
71	24	0	1	73.69%	57.36%	84.57%
85	23	0	1	73.69%	57.36%	84.57%
86	22	1	0	70.34%	53.31%	82.14%
92	21	1	0	66.99%	49.48%	79.61%
113	20	1	0	63.64%	45.81%	76.99%
113	19	0	1	63.64%	45.81%	76.99%
114	18	0	1	63.64%	45.81%	76.99%
167	17	1	0	59.90%	41.69%	74.07%
167	16	0	1	59.90%	41.69%	74.07%
197	15	1	0	55.91%	37.39%	70.91%
197	14	0	1	55.91%	37.39%	70.91%
221	13	1	0	51.61%	32.89%	67.47%
223	12	0	1	51.61%	32.89%	67.47%
225	11	0	1	51.61%	32.89%	67.47%
239	10	1	0	46.45%	27.43%	63.47%
252	9	1	0	41.29%	22.48%	59.19%
252	8	0	1	41.29%	22.48%	59.19%
253	7	0	1	41.29%	22.48%	59.19%
254	6	1	0	34.40%	15.79%	53.97%
254	5	0	1	34.40%	15.79%	53.97%
281	4	0	2	34.40%	15.79%	53.97%
295	2	0	1	34.40%	15.79%	53.97%
300	1	0	1	34.40%	15.79%	53.97%

Abbreviations: CI, confidence interval

Note: Time to first subsequent disease flare is calculated from when patients first meet all three criteria in one assessment (absence of recurrence of GCA signs and symptoms, normalization of ESR, and no CS dose increase) after the first flare. Patients who never experienced a first flare are excluded from the analysis. If a patient had a first flare but never met all three criteria in one assessment after the first flare, the patient will be considered as having a disease flare at Day 0.

Table 26. SELECT-GCA: time to first subsequent flare through Week 52 (FAS1) – upadacitinib 15 mg plus 26-week corticosteroid taper (all patients)

Day	N at Risk	N event	N Censored	S(t)	95% CI

					Lower Bound	Upper Bound
0	52	0	0	100.00%	100.00%	100.00%
0	52	4	0	92.31%	80.79%	97.04%
1	48	0	5	92.31%	80.79%	97.04%
10	43	1	0	90.16%	77.93%	95.79%
15	42	0	1	90.16%	77.93%	95.79%
29	41	2	0	85.76%	72.36%	92.97%
33	39	1	0	83.56%	69.72%	91.45%
44	38	1	0	81.36%	67.15%	89.87%
50	37	0	1	81.36%	67.15%	89.87%
54	36	0	1	81.36%	67.15%	89.87%
57	35	1	0	79.04%	64.43%	88.17%
57	34	0	1	79.04%	64.43%	88.17%
76	33	0	1	79.04%	64.43%	88.17%
85	32	1	0	76.57%	61.53%	86.35%
85	31	0	2	76.57%	61.53%	86.35%
113	29	0	3	76.57%	61.53%	86.35%
127	26	0	1	76.57%	61.53%	86.35%
134	25	1	0	73.51%	57.70%	84.18%
141	24	0	1	73.51%	57.70%	84.18%
144	23	0	1	73.51%	57.70%	84.18%
147	22	0	1	73.51%	57.70%	84.18%
152	21	0	1	73.51%	57.70%	84.18%
157	20	0	1	73.51%	57.70%	84.18%
169	19	0	3	73.51%	57.70%	84.18%
183	16	1	0	68.91%	51.16%	81.32%
190	15	0	1	68.91%	51.16%	81.32%
195	14	1	0	63.99%	44.75%	78.05%
196	13	0	1	63.99%	44.75%	78.05%
197	12	0	2	63.99%	44.75%	78.05%
211	10	0	1	63.99%	44.75%	78.05%
225	9	0	1	63.99%	44.75%	78.05%
227	8	0	1	63.99%	44.75%	78.05%
252	7	0	1	63.99%	44.75%	78.05%
255	6	0	1	63.99%	44.75%	78.05%
280	5	0	1	63.99%	44.75%	78.05%
281	4	0	2	63.99%	44.75%	78.05%
283	2	0	2	63.99%	44.75%	78.05%

Abbreviations: CI, confidence interval

Note: Time to first subsequent disease flare is calculated from when patients first meet all three criteria in one assessment (absence of recurrence of GCA signs and symptoms, normalization of ESR, and no CS dose increase) after the first flare. Patients who never experienced a first flare are excluded from the analysis. If a patient had a first flare but never met all three criteria in one assessment after the first flare, the patient will be considered as having a disease flare at Day 0.

Table 27. SELECT-GCA: time to first subsequent flare through Week 52 (FAS1) – placebo plus 52-week corticosteroid taper (patients with new onset disease)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0						

0								
1								
11								
31								
34								
41								
58								
71								
86								
92								
113								
114								
167								
167								
197								
221								
223								
252								
252								
253								
254								
281								
295								

Abbreviations: CI, confidence interval

Note: Time to first subsequent disease flare is calculated from when patients first meet all three criteria in one assessment (absence of recurrence of GCA signs and symptoms, normalization of ESR, and no CS dose increase) after the first flare.

Patients who never experienced a first flare are excluded from the analysis. If a patient had a first flare but never met all three criteria in one assessment after the first flare, the patient will be considered as having a disease flare at Day 0.

Table 28. SELECT-GCA: time to first subsequent flare through Week 52 (FAS1) – upadacitinib 15 mg plus 26-week corticosteroid taper (patients with new onset disease)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0						
0						
1						
10						
15						
29						
33						
50						
54						
57						
57						
76						
85						
85						
113						
134						

157							
169							
183							
195							
197							
211							
225							
227							
255							
280							
281							
283							

Abbreviations: CI, confidence interval

Note: Time to first subsequent disease flare is calculated from when patients first meet all three criteria in one assessment (absence of recurrence of GCA signs and symptoms, normalization of ESR, and no CS dose increase) after the first flare. Patients who never experienced a first flare are excluded from the analysis. If a patient had a first flare but never met all three criteria in one assessment after the first flare, the patient will be considered as having a disease flare at Day 0.

Table 29. SELECT-GCA: time to first subsequent flare through Week 52 (FAS1) – placebo plus 52-week corticosteroid taper (patients with relapsed disease)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0						
0						
1						
22						
45						
85						
113						
197						
225						
239						
254						
300						

Abbreviations: CI, confidence interval

Note: Time to first subsequent disease flare is calculated from when patients first meet all three criteria in one assessment (absence of recurrence of GCA signs and symptoms, normalization of ESR, and no CS dose increase) after the first flare. Patients who never experienced a first flare are excluded from the analysis. If a patient had a first flare but never met all three criteria in one assessment after the first flare, the patient will be considered as having a disease flare at Day 0.

Table 30. SELECT-GCA: time to first subsequent flare through Week 52 (FAS1) – upadacitinib 15 mg plus 26-week corticosteroid taper (patients with relapsed disease)

Day	N at Risk	N event	N Censored	S(t)	95% CI	
					Lower Bound	Upper Bound
0						
0						

protocol or GC free, for the ITT, the new onset subgroup and the relapsed subgroup (15 Tables). The EAG appreciates that some tables may have relatively few entries for the Period 2 data.

Period 2 data have not presented within this submission. This cohort included patients who received upadacitinib during Period 1 and achieved remission for at least 24 weeks prior to Week 52 (end of Period 1), after which they were re-randomised to either continue upadacitinib or switched to placebo. As such, these patients reflect a pre-selected population with sustained response and are not informative to the economic model.

4) Across Periods 1 and 2 pooled for the time to subsequent flare taking the time of first flare as Day 0, separately for the 5 (A) to (E) patient groups of the previous bullet, separately for the ITT, new onset and relapsed subgroups (15 tables). The EAG appreciates that some tables may have relatively few entries. Please provide the KM data in the following format. It would be much appreciated if this could be supplied within an Excel workbook.

Following to the response provided in question A15.3, period 2 data have not presented within this submission. This cohort included patients who received upadacitinib during Period 1 and achieved remission for at least 24 weeks prior to Week 52 (end of Period 1), after which they were re-randomised to either continue upadacitinib or switched to placebo. As such, these patients reflect a pre-selected population with sustained response and are not informative to the economic model.

A16. In the SELECT-GCA trial, the proportion of patients flare free dropped rapidly for the placebo arm between around 9th to 12th months as shown in Company Submission Figures 13 and 14. Could this have been associated with any factors related to study design or operational/logistic issues?

Patients in the placebo arm of SELECT-GCA received a low dose of corticosteroid of less than 4 mg per day between 9 and 12 months. At this stage, relapse rates substantially increase according to clinical expert opinion and published literature, particularly when the prednisolone dose is below 10 mg per day.¹⁷ This pattern is consistent with GiACTA trial observations,¹ confirming it represents expected clinical progression as opposed to study-specific factors.

Section B: Clarification on cost-effectiveness data

B1. Please explain why the PBO + 52 WK CS-T and UPA 15 + 26 WK CS-T Kaplan-Meier plots shown in Company Submission Figure 7 of the Clinical Effectiveness section differ from those presented in Company Submission Figures 12, 13 and 14 of the Economic Analysis section. Please provide improved Kaplan-Meier plots for PBO + 52 WK CS-T and UPA + 26 WK CS-T using the same dataset used in constructing Figures 12, 13 and 14, include 95% uncertainty in the plots and show a number-at-risk table.

The differences between the KM plots presented in the company submission Section 2.6.1.2, Figure 7 (Clinical Effectiveness) and those in Section 3.3.1.1, Figures 12–14 (Economic Analysis) arise from the handling of patient populations included in the analysis. Specifically, the KM data used in the economic model and in Figures 12–14 censored patients who did not meet the flare criteria at baseline (absence of recurrence of GCA signs and symptoms, normalisation of ESR, and no corticosteroid dose increase), in line with the approach taken during TA518 and consistent with committee preferences.¹

During TA518,¹ concerns were raised that including patients who were not in remission at baseline, as this might bias the primary endpoint of the trial in favour of tocilizumab because it is less likely that people whose disease had not responded to high-dose corticosteroids would achieve remission with the lower tapering doses. As such, to mitigate this risk and to align with prior precedent, patients not in remission at baseline were excluded (i.e., censored) from the KM data used to inform the economic model.

Upon review, we identified that the KM curves initially used in our company submission economic model were based on digitised KM data. This has now been corrected, and updated KM data have been added using the appropriate data. The improved plots (Figure 4, Figure 5 and Figure 6), which include 95% confidence intervals and number-at-risk tables, are provided for both the placebo + 52-week corticosteroid tapering and upadacitinib + 26-week corticosteroid tapering arms. The economic model has also been updated to incorporate these corrected KM data. Note that the extrapolated survival curves informing the economic model were based

on the correct (censored) dataset, so no changes to the extrapolation method were necessary, and consequently the outcomes remained unchanged. Only the plotted KM data has been updated; all model results remain unchanged.

Figure 4. SELECT-GCA Kaplan-Meier Curves for Time to First Disease Flare Through Week 52 (FAS1)

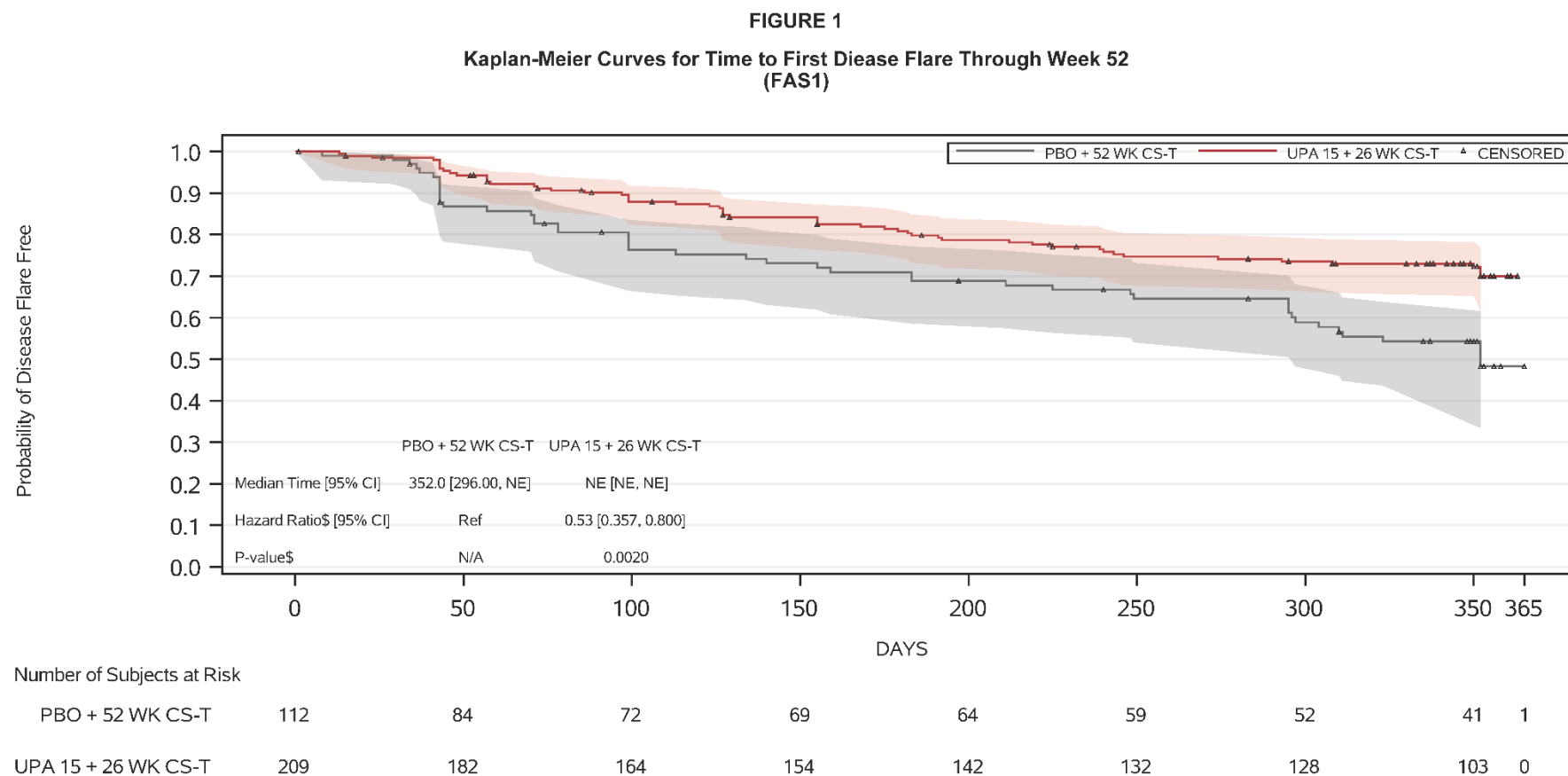


Figure 5. SELECT-GCA Kaplan-Meier Curves for Time to First Disease Flare Through Week 52 (new onset population)



Figure 6. SELECT-GCA Kaplan-Meier Curves for Time to First Disease Flare Through Week 52 (relapsed population)



B2. In submission section 3.2 there is repeated reference to “clinical opinion” or “confirmation by clinicians” and other phrasing such as “validation by ...”. Please list ALL instances of this type of phraseology throughout section 3.2.

Table 31 lists all instances where assumptions in the company submission Section 3.2 are supported by clinical opinion.

Table 31. Instances where assumptions in the company submission Section 3.2 are supported by clinical opinion

Section 3.2	Validation method	Supported by Literature
'The duration of flare was assumed to be 4 weeks, following the committee preferred duration reported in TA518 and validated through consultation with clinical experts '	Advisory board	Committee preferred duration reported in TA518 ¹
'In the aftermath of a flare, clinical expert advice was followed regarding the immediate likelihood of a subsequent flare and the accompanying corticosteroid dose. It is assumed that during the 4 weeks following flare, patients are not subject to the probability of a further flare and instead revert to their last effective corticosteroid dose, defined as that received in the week preceding the flare for the 4-week flare period.'	Advisory board	BSR guidelines ¹⁸
' Clinical experts consulted at the advisory board noted that of patients experiencing flare, approximately 20% of these will be severe'	Advisory board	In the TOCSTOP study in a cohort of relapsing and refractory GCA patients, 33.6% of relapses were severe (as defined by EULAR criteria). ¹⁹ The assumption that 20% of all GCA patients would experience a severe flare broadly aligns with this literature, as this number accounts also accounts for new onset GCA patients who are expected to have lower severe relapse rate.

'The cumulative corticosteroid dose in the model is estimated in three steps: (1) calculating the average corticosteroid dose for each health state; (2) multiplying that average dose by the proportion of patients in each health state per cycle; and (3) summing the cumulative dose from previous and current cycles. Based on this evolving cumulative dose, the model applies AE incidence rates specific to steroid dosage bands, in line with both real-world data and thresholds validated by UK clinicians.'	Advisory board	Data was sourced from MarketScan real-world evidence study²⁰ The methodology for deriving corticosteroid related AEs was accepted in TA518¹ Literature supports the mean daily corticosteroid doses thresholds used in the model²¹
'Emerging evidence indicates that treatment with an active agent beyond one year is often necessary to maintain disease control and prevent relapse. Reflecting this and in line with clinical feedback, the base-case analysis assumes a 24-month treatment duration for upadacitinib.'	Advisory board	TOCSTOP study indicates that treatment with an active agent beyond one year is often necessary to maintain disease control and prevent relapse.¹⁹

Abbreviations: AE, adverse event; BSR, British Society for Rheumatology; EULAR, European Alliance of Associations for Rheumatology; GCA, giant cell arteritis; TA, technology appraisal

B3. Priority question No clinical data on Time To Subsequent Flare (TTSF) appears to have been presented and little information is presented about Table 28 and appendices Tables 59 and 60. Please provide full details of what data, including any Period 2 data, is used to generate these tables together with the time period they relate to. Please state the definition of flare for this analysis if it differs from that used for the time to first flare analysis. Please provide this data in sufficient detail to replicate these Poisson regressions, split by the 5 (A) to (E) patient groups of the last bullet of the KM data request above. What other regressions were considered, such as the negative binomial regression, which were quantified and why was the Poisson regression preferred to them. If individual patients who flared more than three times (1st, 2nd, 3rd...) could contribute more than one flare to TTSF analyses please state how many patients did so, split by arm, separately for the ITT, new onset and relapsed cohorts. If the estimates of Table 28 and Appendices Tables 59 and 60 include Period 2 data, please present their equivalents using only Period 1 data.

In the SELECT-GCA trial, in order for patients to meet the definition of a flare, patients were required to be in remission at a minimum of one prior visit. Remission

was defined as the absence of recurrence of GCA signs and symptoms, normalization of ESR, and no increase in corticosteroid dose. A flare during Period 1 was defined as an event determined by the investigator to represent a recurrence of GCA signs or symptoms, or an ESR measurement > 30mm/hr attributable to GCA, that required an increase in corticosteroid dose. Patients could experience more than one flare during the study period if they returned to remission for at least one visit following the initial flare and then met the definition of a flare at a subsequent visit as defined above. Flares could occur during either scheduled or unscheduled visits.

Table 32, Table 33, and Table 34 provide data on the number of flares experienced by patients during period 1. The number of flares was recorded during the 52-week period, excluding the initial flare. Since patients may experience multiple flares during Period 1, a method suitable for count data (Poisson regression) was employed in line with the method used in TA518. In the Poisson regression, the number of disease flares was used as the response variable, and the log of the follow-up time in weeks was used as an offset. Furthermore, the deviance and degrees of freedom were evaluated and showed that the data were under-dispersed (degrees of freedom ratio < 1). To validate results, a negative binomial regression was also conducted, and estimates remained unchanged.

Table 32. Summary of number of subsequent flares in period 1, ITT population

Number of flares	PBO + 52 WK CS-T (N = 44) n (%)	UPA + 26 WK CS-T (N = 52) n (%)
0		
1		
2		
3		
> 3		

Abbreviations: CS-T, corticosteroid taper; ITT intention-to-treat; n, number of observations; PBO, placebo; UPA, upadacitinib

Table 33. Summary of number of subsequent flares in period 1, new onset population

Number of flares	PBO + 52 WK CS-T (N = 29) n (%)	UPA + 26 WK CS-T (N = 35) n (%)
0		
1		
2		
3		
> 3		

Abbreviations: CS-T, corticosteroid taper; ITT intention-to-treat; n, number of observations; PBO, placebo; UPA, upadacitinib

Table 34. Summary of number of subsequent flares in period 1, relapse population

Number of flares	PBO + 52 WK CS-T (N = 15) n (%)	UPA + 26 WK CS-T (N = 17) n (%)
0		
1		
2		
3		
> 3		

Abbreviations: CS-T, corticosteroid taper; ITT intention-to-treat; n, number of observations; PBO, placebo; UPA, upadacitinib

B4. Priority question. The following questions all relate to the AbbVie sponsored and co-authored MarketScan analysis (ref 44), AbbVie being stated as having access to the underlying data. For this question all table and figure references are to those within reference 44 unless otherwise stated.

1) Please provide any supplementary tables and figures.

A manuscript detailing this study has been provided as a reference and includes all the supplementary materials.²⁰

2) Please clarify if the Merative™ MarketScan® databases include data on those with insurance or only on those with insurance who have made a claim. Please clarify if the CC1 and/or the CC2 cohort data was limited to those who have made a claim during the period Jan 1 2010 and Dec 31 2019.

The Merative MarketScan database provides comprehensive information on patients with insurance coverage, regardless of their claim status.²⁰ The total number of patients is derived from the enrolment file, which includes individuals who may not have had any claims during the study period. In the study, two control cohorts are defined. Control cohort 1 (CC1) included patients with no GCA and no use of oral corticosteroids (GCs). Control cohort 2 (CC2) included patients with no diagnosis of GCA. Patients who had not made a claim were not excluded from either cohort.

To identify patients in CC1, inpatient and outpatient utilization files from Truven dataset were queried to exclude individuals with diagnosis of PMR, GCA, or any use of oral corticosteroids between January 1, 2009, and December 31, 2020. Each patient was assigned a random index date between January 1, 2010, and December 31, 2019. Additional inclusion criteria required patients to be ≥ 50 years old on the

index date and to have at least 12-months of continuous enrolment with both medical and pharmacy benefits before and after the index date. From the eligible population, 5% were randomly selected to form the final CC1 cohort. Patients in CC2 were identified using the same methodology as CC1, with the exception that the exclusion criterion for oral corticosteroids use was not applied.

3) Please clarify how those with data for less than 12 months were handled in terms of calculating their mean daily steroid dose and the contribution of this to the overall mean daily steroid dose distribution.

Patients who did not have continuous insurance enrolment for 12-months during the follow-up period were excluded. Including only those with full 12-month coverage ensured complete capture of their corticosteroid prescription data.

4) Please confirm that Table 3 presents mean daily GC doses not weighted by duration of steroid use; i.e as per Clarification Question A11 above. The EAG interpretation of Table 3 is that it excludes those with less than 25 months follow up and excludes those with more than 36 months follow up, and that among these patients 1,956 patients received GC during the 1st year, 961 received GC during the 2nd year and 709 received GC during the 3rd year. Please present data in this format using the mean daily steroid cutoffs of Raw Safety cells C263:R314 separately for those with only 0-12 months follow-up, only 13-24 months follow-up, only 25-36 months follow-up, only 37-48 months follow-up and only 49-60 months follow-up, augmenting this with columns for mean dosing during 37-48 months and during 49-60 follow-up as necessary (5 Tables).

It is correct that Table 3 excludes patients with less than 25-months of follow up. However, Table 3 does not exclude patients with more than 36-months of follow up. The two different follow up time frames were selected to study corticosteroid dose in year 2 and 3. As requested the mean daily corticosteroid dose for 1–12 months, 13–

24 months, 25–36 months, 37–48 months, and 49–60 month is provided in Table 35, Table 36, Table 37, Table 38, and Table 39, respectively.

Table 35. Mean daily corticosteroid dose for patients 1–12 months post corticosteroid initiation

Patients with 1–12 months of follow-up post CS initiation (N, %)	Oral CS sub-cohort 01–12 months follow-up	
	N	%
Average daily dose over 01–12 months of exposure (N, %), among patients (any CS usage)		
Low dose: 0 to ≤ 5 mg		
> 5 to ≤ 10 mg		
> 10 to ≤ 20 mg		
> 20 to ≤ 40 mg		
> 40 mg		

Abbreviations: CS, corticosteroid; N, number of observations

Table 36. Mean daily corticosteroid dose for patients 13–24 months post corticosteroid initiation

Patients with 13–24 months of follow-up post CS initiation (N, %)	Oral CS sub-cohort 13–24 months follow-up	
	N	%
Average daily dose over 13–24 months of exposure (N, %), among patients (any CS usage)		
Low dose: 0 to ≤ 5 mg		
> 5 to ≤ 10 mg		
> 10 to ≤ 20 mg		
> 20 to ≤ 40 mg		
> 40 mg		

Abbreviations: CS, corticosteroid; N, number of observations

Table 37. Mean daily corticosteroid dose for patients 25–36 months post corticosteroid initiation

Patients with 25–36 months of follow-up post CS initiation (N, %)	Oral CS sub-cohort 25–36 months follow-up	
	N	%
Average daily dose over 25–36 months of exposure (N, %), among patients (any CS usage)		
Low dose: 0 to ≤ 5 mg		
> 5 to ≤ 10 mg		
> 10 to ≤ 20 mg		
> 20 to ≤ 40 mg		
> 40 mg		

Abbreviations: CS, corticosteroid; N, number of observations

Table 38. Mean daily corticosteroid dose for patients 37-48 months post corticosteroid initiation

Patients with 37–48 months of follow-up post CS initiation (N, %)	Oral CS sub-cohort 37–48 months follow-up	
	N	%
Average daily dose over 37–48 months of exposure (N, %), among patients (any CS usage)	■	I
Low dose: 0 to ≤ 5 mg	■	■
> 5 to ≤ 10 mg	■	■
> 10 to ≤ 20 mg	■	■
> 20 to ≤ 40 mg	I	■
> 40 mg	I	■

Abbreviations: CS, corticosteroid; N, number of observations

Table 39. Mean daily corticosteroid dose for patients 49-60 months post corticosteroid initiation

Patients with 49–60 months of follow-up post CS initiation (N, %)	Oral CS sub-cohort 49–60 months follow-up	
	N	%
Average daily dose over 49–60 months of exposure (N, %), among patients (any CS usage)	■	I
Low dose: 0 to ≤ 5 mg	■	■
> 5 to ≤ 10 mg	■	■
> 10 to ≤ 20 mg	■	■
> 20 to ≤ 40 mg	I	■
> 40 mg	I	■

Abbreviations: CS, corticosteroid; N, number of observations

5) Within the N=4,114 GCA+GC cohort what proportion were ICD10 M31.6 and what proportion were ICD10 M31.5?

All patients had a diagnosis of M31.6 in the cohort which corresponds to a GCA diagnosis. ■ of patients had a diagnosis code of ICD-10 CM M31.5, ICD-10 CM M35.3 or ICD-9-CM 725 which corresponds to PMR diagnosis (Table 40).

Table 40. Proportion of GCA patients with and without PMR

GCA patients with/without PMR	N (%)
Patients with GCA diagnosis	■
GCA patient with PMR during 1-year baseline or on the index date	■
GCA only patients during 1-year baseline or on the index date	■

Abbreviations: GCA, giant cell arteritis; N, number of observations; PMR, polymyalgia rheumatica

6) Please provide the ICD10 codes or where not applicable the definition of each GRAE listed in Table 4.

Please see Appendix B4.6

- 7) **Please separately split the 620 GCA+GC, the 279 CC1 and the 300 CC2 patients of Table 4 who developed psychiatric events into the lowest level of ICD10 codes possible or if this cannot be done into the most disaggregate form possible.**

Please see Appendix B4.7

- 8) **Please present the prevalences of the complications of Table 4 at the GCA Index Date separately for the GCA GC, CC1 and CC2 cohorts. Please also outline if these Index Date baseline prevalences contribute to the occurrence of GRAEs of Table 4.**

Please see Appendix B4.8

- 9) **Please tabulate the values of Figure 2 including the upper and lower error bar values. Given that the data includes all N=4,114 for each cohort please clarify what period the dosing classification of low, medium, high and very high relates to.**

Please see Appendix B4.9

- 10) **Please provide the equivalent of Table 4 for the GCA GC cohort split by the mean daily steroid dose 0-12 months categories of Figure 2.**

Please see Appendix B4.10

- 11) **The Raw Safety cells C263:R314 use different mean steroid daily dose cutoffs than those presented in reference 44. Why is this?**

The original stratification of mean daily corticosteroid doses (low: > 0 to ≤ 7.5 mg; medium: > 7.5 to ≤ 20 mg; high: > 20 to ≤ 40 mg; very high: > 40 mg) shown in reference 44 was adapted to reflect UK clinical practice. During advisory board discussions with UK clinical experts, the validity of these thresholds was questioned in the context of contemporary GCA management. Clinicians indicated that these

groupings did not accurately reflect the way steroid burden is assessed in clinical practice, particularly in the low and medium dose as these ranges were too broad

Experts suggested the following thresholds: low dose (≤ 5 mg), medium dose (> 5 mg to ≤ 10 mg), high dose (> 10 mg to ≤ 20 mg), very high dose (> 20 mg to ≤ 40 mg), and extremely high dose (> 40 mg). These recommendations align with findings from a multidisciplinary European League Against Rheumatism task force, which indicated that long-term dosages of ≤ 5 mg prednisone equivalent per day carry a low risk of harm, whereas dosages > 10 mg/day significantly increase the risk.²¹ In response to this feedback and supporting literature, the model was updated to adopt these revised dose categories and the adverse event data were re-stratified accordingly.

12) Please present the equivalent of the patient numbers within Raw Safety cells C263:R314, retaining the mean daily steroid dose cutoffs of Raw Safety cells C263:R314 separately for cases newly incident during (1) months 12-24, (2) months 25-36, (3) months 37-48 and (4) months 49-60 also presenting the total number of patients that underlie these estimates as in cells C264:R264. Please present this separately for two analyses: (1) calculating the mean daily steroid dose from baseline and (2) calculating the mean daily steroid dose for the year newly incident cases are being reported for, not weighting (1) or (2) by duration of steroid use; i.e. as per Clarification Question A11 above. Please also present the corresponding newly incident cases separately for the CC1 and CC2 cohort.

The mean dose per corticosteroid dose threshold cannot be estimated because the RWE study was conducted retrospectively, lacking insights into the tapering schedules of patients, which would affect the mean daily dose. Nevertheless, the study collected cumulative mean steroid doses for the following follow-up durations: 0-12 months, 1-24 months, 1-36 months, and 1-60 months, presented in Table 41 below. The number of patients per average daily dose stratified by the mean daily steroid dose cutoffs of Raw_Safety cells C263:R314 is included in Appendix B4.12.

Both analyses are only available for the oral corticosteroids sub-cohort, as CC1 has no corticosteroid use, and in CC2, only 1.92% of patients had corticosteroids.

Table 41. Cumulative mean corticosteroid dose

	1-12 months follow-up	1-24 months follow-up	1-36 months follow-up	1-60 months follow-up
N				
Cumulative mean dose in mg (SD)				

B5. Company Submission Table 4 notes that in SELECT-GCA during Period 1 upon flare patients should stop the protocol defined taper and revert to a minimum of 20mg steroid. Why does the economic model assume the next highest dose for non-severe flares rather than 20mg?

In SELECT-GCA, subjects who experienced a disease flare during the blinded protocol-defined CS taper received open-label escape therapy with prednisone or prednisolone starting with at least 20 mg/day at the discretion of the investigator. This methodology for escape therapy is consistent with the GiACTA study published previously. Clinical feedback indicated that patients experiencing a non-severe flare that were previously stable on a lower dose of corticosteroids would revert to the previous higher corticosteroid dose, taking into account individual patient characteristics and disease symptoms, which is in line with national and international GCA guidelines¹⁸. For example, if a patient was stable on 7.5 mg and experienced a flare on 5 mg, the patient would revert to 7.5 mg.

Aligned with this feedback and the guidelines,¹⁸ the submitted economic model assumes that patients with non-severe flares revert to the next highest dose relative to their pre-flare tapering schedule, rather than reverting to 20 mg.

A scenario analysis is presented where the economic model aligns with the SELECT-GCA protocol during Period 1, where patients revert to a minimum dose of 20 mg upon a non-severe flare. This approach ensures consistency with trial-defined treatment rules and provides a protocol-aligned estimate of corticosteroid exposure for modelling purposes. As can be seen in Table 42, incremental costs are further

reduced and QALYs are improved versus the updated base case analysis (Table 46), due to increased use of corticosteroids

Table 42. Scenario analysis: reversion to a minimum corticosteroid dose of 20 mg upon disease flare

	Upadacitinib	Corticosteroids	Incremental
QALYs	■	■	■
Costs (£)	■	■	■
ICER (£/QALY)			Dominant

*applies updates conducted as part of B8, B9 and B13

B6. Please provide a copy of the full statistical report that underlies Company Submission Table 35 including the consideration of choice of models and control variables and why the final model was chosen. How was flare defined in terms of symptoms, quantified elements such ESR levels and the time period around the EQ-5D data collection points and how does this tally with that of Company Submission Figure 14?

In the SELECT-GCA trial, EQ-5D 5L data was collected at baseline and at weeks 8, 24, and 48, then transformed into EQ-5D 3L data using the Van Hout algorithm. At each visit where EQ-5D data was present, the patient's flare/remission status was determined. The definition of flare followed that used in the SELECT-GCA study. To categorise a status as no flare, the patient had to achieve complete remission at the visit. The mean EQ-5D-3L data was analysed through a Generalised Estimating Equation (GEE), with flare status as the independent variable, while adjusting for baseline EQ-5D values. The GEE model utilised a normal distribution and identity link function, with an unstructured correlation matrix to adjust for within-person correlation. Complete case analysis was conducted, excluding visits with missing EQ-5D data.

Appendix B6 provides all available statistical data for this analysis.

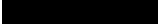
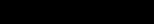
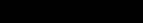
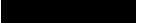
B7. Please provide the N patients eligible to report, n patients reporting EQ-5D, mean EQ-5D and the standard deviation (not standard error) around the mean EQ-5D separately by arm for the ITT, and the new onset and relapsed subgroups split by whether the reporting patients are in flare or in remission (6

Tables). Note that the EAG has based the data collection points on Appendix D of the study protocol.

The requested EQ-5D data for the SELECT-GCA trial ITT population, and the new onset and relapsed subgroups, separated by whether the reporting patients were in flare or no flare is provided in Table 43, Table 44, and Table 45.

As mentioned in the response to question B3, in order for patients to meet the definition of flare, patients were required to be in remission at a minimum of one prior visit. Patients who did not meet all three remission criteria (absence of GCA signs and symptoms, normalisation of ESR, and no increase in corticosteroid dose) during the treatment period are excluded from all analysis. For patients who did meet all three criteria to be considered in remission, any EQ-5D values recorded prior to the date on which all three criteria were first met are excluded from the analysis, as flare status cannot be assigned until that point. Since the first assessment of these criteria occurred after treatment initiation, baseline EQ-5D values cannot be associated with a flare status. Flare status is dynamic and may change from visit to visit for a given patient. The time points when EQ5D-5L data is collected would not necessarily match when a subject experiences a flare or even within 4 weeks of experiencing a flare. For example, if a patient experiences a flare at week 26 of the trial, and EQ5D data is collected much later in the trial i.e. at week 52 then it is difficult to capture the impact of a flare on utility after 26 weeks

Table 43. Summary of EQ-5D-3L (UK Value Set) in Period 1, ITT population

Flare Status*	PBO + 52 WK CS-T (N=122)	UPA + 26 WK CS-T (N=209)
Flare		
Week 8		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Week 24		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Week 52		
N		

Mean (SD)		
Median		
Q1, Q3		
Min, Max		
No Flare		
Week 8		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Week 24		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Week 52		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		

*An EQ-5D-3L observation is assigned as 'Flare' if the subject was classified as having a flare at that analysis visit. Otherwise, the EQ-5D-3L observation is assigned as "No Flare".

Abbreviations: CS-T, corticosteroid taper; N, number of observations; PBO, placebo; Q1, first quartile; Q3, third quartile; SD, standard deviation; UPA, upadacitinib; WK, week

Table 44. Summary of EQ-5D-3L (UK Value Set) in Period 1, new onset disease

Flare Status*	PBO + 52 WK CS-T (N=76)	UPA + 26 WK CS-T (N=148)
Flare		
Week 8		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Week 24		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Week 52		
N		
Mean (SD)		
Median		

Q1, Q3		
Min, Max		
No Flare		
Week 8		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Week 24		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Week 52		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		

*An EQ-5D-3L observation is assigned as 'Flare' if the subject was classified as having a flare at that analysis visit. Otherwise, the EQ-5D-3L observation is assigned as "No Flare".

Abbreviations: CS-T, corticosteroid taper; N, number of observations; NA, not applicable; PBO, placebo; Q1, first quartile; Q3, third quartile; SD, standard deviation; UPA, upadacitinib; WK, week

Table 45. Summary of EQ-5D-3L (UK Value Set) in Period 1, relapsing disease

Flare Status*	PBO + 52 WK CS-T (N=36)	UPA + 26 WK CS-T (N=61)
Flare		
Week 8		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Week 24		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Week 52		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
No Flare		

Week 8		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Week 24		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		
Week 52		
N		
Mean (SD)		
Median		
Q1, Q3		
Min, Max		

*An EQ-5D-3L observation is assigned as 'Flare' if the subject was classified as having a flare at that analysis visit. Otherwise, the EQ-5D-3L observation is assigned as "No Flare".

Abbreviations: CS-T, corticosteroid taper; N, number of observations; NA, not applicable; PBO, placebo; Q1, first quartile; Q3, third quartile; SD, standard deviation; UPA, upadacitinib; WK, week.

B8. Within Trace_Tx1 cell C021 has the divisor $SUM(AC20*(1-J21)*K21, SUM(\$AH20:\$CG20)*\$L21*(1-I21), (CH20*(1-J21)*\$L21))$. Cell AD21 is $(AC20*(1-J20)*K20) + (SUM(\$AH20:\$CG20)*\$L20*(1-I20)) + (\$CH20*\$L20*(1-J20))$. Why does the former use row 21 values for the probabilities of flares and survival while the latter uses the row 20 values? Please provide an intuitive account of why these two quantities are not equal.

The use of values in row 21 for the probabilities of flare and survival are incorrect as these should use row 20 values. This has been corrected throughout column CO and a new model included alongside this response (Appendix B8). An updated analysis is provided in Table 46.

Table 46. Economic model correction

	Upadacitinib	Corticosteroids	Incremental
QALYs			
Costs (£)			
ICER (£/QALY)			Dominant

* Applies updates conducted as part of B8, B9 and B13

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

B9. Please provide an intuitive account of why the mean steroid dose in Trace_Tx1 cell CS25 is higher than that in cell CR24.

Columns CO to CR reflect the four tunnel states that patients go through during a flare. The intention of the formula in column CO, which is then carried over to columns CP, CQ, and CR, is to establish the average corticosteroid dose that patients revert to after experiencing a flare. This calculation includes the dose required for those who have experienced a severe flare.

Column CS reflects the first week of post flare remission. In column CS, the formula looks at the average obtained in column CR and assigns a value to it from the tapering schedule (columns P:Z), with the value assigned being the next highest dose if the exact average is not available in the tapering schedule.

On reflection, the company understands that this may cause some confusion and therefore have amended the formula in column CO so that this now includes assigning a value from the tapering schedule, thus combining the two formulae described above into one. This has been completed in the updated model that has been included alongside this response.

B10. Please provide the baseline steroid dosing data for the newly diagnosed subgroup and the relapsed subgroup equivalent to Raw_DrugCosts cells E190:H194.

The baseline corticosteroid dosing data for the newly diagnosed subgroup and the relapsed subgroup are shown in Table 47 and Table 48, respectively. These values have been added to the cost-effectiveness model and are used when the subgroups are selected. The updated outcomes are provided in Appendix B10.

Table 47. Baseline steroid dosing data in newly diagnosed patients

Starting dose	Upadacitinib 15mg		Placebo	
	N	%	N	%
20	■	■	■	■
30	■	■	■	■
40	■	■	■	■
50	■	■	■	■
60	■	■	■	■

Abbreviations: N, number of observations

Table 48. Baseline steroid dosing data in relapsed patients

Starting dose	Upadacitinib 15mg		Placebo	
	N	%	N	%
20	■	■	■	■
30	■	■	■	■
40	■	■	■	■
50	■	■	■	■
60	■	■	■	■

Abbreviations: N, number of observations

B11. Please provide the number eligible to report and the number completing the HCRU questionnaire (including if possible those reporting no HCRU for the relevant period) and the total number of health care profession visits (HCPV), ER visits (ERV) and hospital admissions (HA) split by arm assessed by the HCRU questionnaire at week 24, 52 and 164. For week 164 please pool those who receiving upadacitinib 15mg during Period 1 and continued to do so in Period 2. Please also pool those receiving placebo in Period 2. Please also clarify if “the last protocol required visit” refers to the last HCRU questionnaire administration or something else, and if so what.

This response assumes that the EAG refers to week 104, as opposed to week 164, as the study does not extend to week 164.

A summary of those eligible to report, the number of those who completed the HCRU questionnaire, and the total number of health care professional visits, ER visits, and hospital admissions are provided in Table 48. The management costs per flare event included in the economic model are based on data from the UK market research study used in TA518¹. This approach was taken as, due to controlled trial settings, HCRU in SELECT-GCA does not accurately reflect what is expected to be seen in clinical practice.

Table 49. SELECT-GCA: summary of HCRU questionnaire

	Upadacitinib 15mg					Placebo				
Week	N eligible to report	n completing HCRU quest	Total n HCPV	Total n ERV	Total n HA	N eligible to report	n completing HCRU quest	Total n HCPV	Total n ERV	Total n HA
24	■	■	■	■	■	■	■	■	■	■
52	■	■	■	■	■	■	■	■	■	■
104	■	■	■	■	■	■	■	■	■	■

Abbreviations: ERV, emergency room visit; HA, hospital admissions; HCPV, health-care practitioner visits; N, number of observations

B12. It would be appreciated if a spreadsheet performing the calculations described in the past paragraph of Page 150 starting “The disease management costs...” could be provided.

Appendix B12 has been provided alongside this response document that performs the calculations requested. While data were available for healthcare resource use for patients who were pre-flare remission on- and off-corticosteroids, data for post-flare remission on- and off-corticosteroid subgroups were not separately reported and were reported for post-flare on-corticosteroid only (UK market research study conducted by Roche [Research Partnerships 2017], reported in TA518).¹ Therefore, an assumption was made that the ratio of patients on versus off corticosteroids in the post-flare remission state mirrored that observed in the pre-flare remission state. Specifically, the ratio was applied to the post-flare (on-corticosteroid) remission proportions to derive corresponding proportions for the post-flare off-corticosteroid subgroup.

B13. For each NHS Reference cost of Tables 44, 48, 49 and 50 please state the currency codes, specialty, type of patient engagement, e.g. consultant face to face followup, setting. e.g. day patient and OP included, etc and the basis of

the calculation if it is anything other than a weighted average of the included NHS Reference average costs sufficient to identify the inputs and calculate the costs of Tables 44, 48, 49 and 50. The Raw_HCRU sheet appears to contain some but not all of this information. If it would be easier to supply this as a fully documented excel spreadsheet this would be very welcome.

As requested, Appendix B13 has been provided that sets out Tables 44, 48, 49, and 50 and individually sets out the equations that are used to generate the weighted average for each component sourced from NHS Reference costs. For further clarity, additional detail was provided in the economic model in the Raw_Safety sheet.

As each component was assessed, minor discrepancies were found in Table 49. These have been marked out in the spreadsheet and have been corrected in the new model which accompanies this document. The impacted inputs were as follows: GI perforation, Glaucoma, Sepsis, and Ulcer/GI bleed.

An updated base case analysis has been provided in Table 46.

B14. Please provide copies of all reports that include results, both qualitative and quantitative, from the February 2025 Advisory boards together with all associated questionnaires or briefing materials sent to or seen by participants. Please also provide anonymized details of each participants' field of expertise, highest qualification, employment (e.g. practicing consultant specializing in GCA, generalist health economist) and any other details though to be relevant.

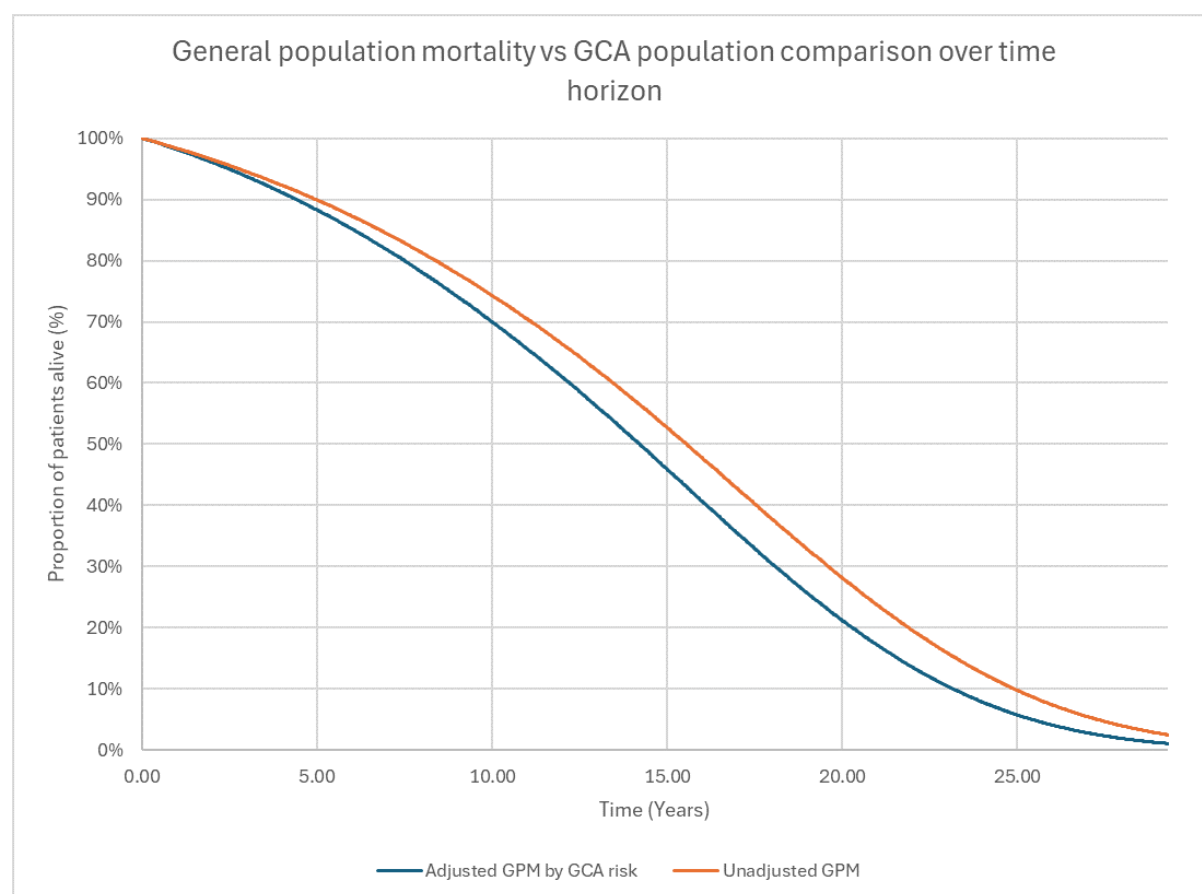
The Advisory Board report has been provided in Appendix B14. Ten consultant rheumatologists were approached to participate in the advisory board.

Rheumatologists were selected based on their expertise in treating patients with GCA. Six out of 10 clinicians approached agreed to participate, representing different expert centres within England and Scotland. Two health economists were approached to participate in this advisory board. They were selected by AbbVie based on their expertise in health economic modelling. Further details relating to the participants expertise and other advisory board related materials that aided discussion on the day can be found in the Appendix within the Advisory Board report.

B15. Please supply graphical representation of the all-cause mortality used in the economic model.

Figure 7 provides a graphical representation of all-cause mortality used in the economic model, showing the proportion of the cohort alive over time for unadjusted general population mortality (GPM) and GPM adjusted for excess risk due to GCA. These figures reflect the application of UK life table data (ONS 2020–2022) and literature-based risk adjustments for GCA-related mortality, as described in Section 3.3.1.3 of the company submission. It should be noted that approximately ■■■ of the GCA cohort remain alive at the end of the model time horizon, compared with around ■■■ in the GPM population.

Figure 7. Modelled all-cause mortality



Section C: Textual clarification and additional points

C1. In Appendix B, page 53: In addition to the clinical trial evidence identified and reported on (primary purpose of the SLR), the current SLR identified 37 reports corresponding to 33 observational studies that report adverse event

data among GCA patients taking glucocorticoids. Could you explain the search methodology and study selection process?

A single search strategy was developed to identify clinical trial evidence of GCA interventions and observational studies of safety and adverse events. The methodology is described in the company submission appendix B. The additional search for safety and adverse event data in observational studies ensured comprehensiveness by capturing the relevant real-world data. All results from the clinical searches were screened independently in Covidence according to the PICOS criteria.

To identify the subset of observational studies meeting PICOS criteria that report corticosteroid-related AEs, full-text records of observational studies meeting PICOS criteria were reviewed by two independent researchers to determine whether any corticosteroid-related AE data were present. Disagreements between researchers were resolved by discussion or by review with a third researcher. An observational study was not selected for extraction of adverse event data if researchers agreed that corticosteroid-related AE data were not reported.

C2. Please supply a full list with definitions of all abbreviations and acronyms used in the submission.

As requested, please find below list of abbreviations and acronyms used in the submission.

AE	adverse events
AESIs	adverse events of special interest
AIC	Akaike Information Criterion
AO	as observed
BMI	body mass index
BNF	British National Formulary
BSR	British Society for Rheumatology
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	cost-effectiveness analysis
CEAF	cost-effectiveness acceptability frontier
CHMP	Committee for Medical Products for Human Use
CI	confidence interval
CNS	central nervous system
CPRD	Clinical Practice Research Datalink
CRP	C-reactive protein
CS	corticosteroids
CSR	clinical study report

CS-T	corticosteroid taper
CTA	computed tomography angiography
CTCAE	Common Terminology Criteria for Adverse Events
CUA	cost-utility analysis
DB	double blind
DMARDs	disease-modifying antirheumatic drugs
DSA	deterministic sensitivity analysis
eMIT	drugs and pharmaceuticals electronic market information tool
EQ-5D-5L	EuroQoL Five Dimensions Five Levels Questionnaire
ESR	erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
FACIT	Functional Assessment of Chronic Illness Therapy
GBP	Great British Pound
GC	glucocorticoids
GCA	Giant Cell Arteritis
GI	gastrointestinal
GIRFT	Getting it Right First Time
GP	General Practitioner
HAS	Haute Autorité de Santé
HCP	healthcare professional
HCRU	Healthcare Resource Utilisation
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IFN- γ	interferon- γ
IL-6	interleukin-6
INAHTA	International Network of Agencies for Health Technology Assessment
Inc	incremental
IOP	intraocular pressure
IRP	International Recognition Procedure
IRT	interactive response technology
ITT	intention-to-treat
IV	intravenous
JAK	Janus Kinase
JAKi	Janus Kinase inhibitor
KM	Kaplan-Meier
LS	least squares
LYG	life years gained
MACE	major adverse cardiovascular events
mAb	monoclonal antibody
MHRA	Medicines and Healthcare products Regulatory Agency
MI	multiple imputation
MIMS	Monthly Index of Medical Specialities
MRA	magnetic resonance angiography
NHB	net health benefit
NHS	National Health Service

NHSE	NHS England Specialised Commissioning
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	network meta-analysis
NMB	net monetary benefit
NMSC	nonmelanoma skin cancer
NS	not significant
N/A	not applicable
OD	once daily
PAR	public assessment report
PAS	patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PBO	placebo
PCS	Physical Component Summary
PE	point estimate
PET	positron emission tomography
PGA	Patient Global Assessment
PGIC	Patients' Global Impression of Change
PMR	polymyalgia rheumatica
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PT	preferred term
QALY	quality-adjusted life year
QoL	quality of life
QW	once a week
R	randomization
RR	relative risk
RWE	real-world evidence
SE	standard error
SF-36	36-item Short Form Quality of Life Questionnaire
SLR	systematic literature review
SMC	Scottish Medicines Consortium
SmPC	summary of product characteristics
SMR	Standardised mortality ratio
SOC	system, organ, class
SoC	standard of care
STAT	signal transducers and activators of transcription
TA	technology appraisal
TAB	temporal artery biopsy
TB	tuberculosis
TEAEs	treatment-emergent adverse events
Th	T helper
TOCI	Tocilizumab
TTFF	time to first flare

TSQM	Treatment Satisfaction Questionnaire for Medication
TYK	Tyrosine kinase
UK	United Kingdom
UPA	upadacitinib
VAS	visual analogue scale
VTE	venous thromboembolism
WK	week
WTP	willingness-to-pay

C3: Additional clarification question around the method of the unpublished paper by Curtis et al (Ref 44 of the Company submission). The paper states that “Patients had to have at least 12 months’ continuous enrolment after glucocorticoid initiation and had received ≥ 30 -days, but ≤ 360 -days, supply during the 12-month post-index period”. Does this mean that patients with 361 days or more continuous steroid use post GCA index date; i.e. whose steroid use was ongoing for one year or more after GCA index date, were excluded from the analysis? If so, how many patients were excluded for this reason? Similarly, does this mean that patients with a steroid index date 90 days prior to the GCA index date with 361 days or more continuous steroid use since the steroid index date but who then stopped steroid treatment before one year post GCA index date were excluded from the analysis? If so, how many patients were excluded for this reason? Please also clarify if this applies to the company analyses presented in Raw_Safety D266:R314.

It is acknowledged that the statement is confusing. The study required patients to receive a supply greater than 30 days, but less than 360 days, applied to an individual prescription, not to corticosteroid use in follow-ups. In claims databases, sometimes there are errors in reporting days’ supply for prescriptions; therefore, based on typical quantities of prescribed corticosteroid, this condition seeks to avoid these errors. Nevertheless, applying these ranges did not impact results, as ■■■ of prescriptions were less than 30 days, and ■■■ was greater than 360 days supply.

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Single Technology Appraisal
Upadacitinib for treating giant cell arteritis [ID6299]
Patient Organisation Submission

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. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	PMRGCAuk
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are a member based charity providing support and information to those with polymyalgia rheumatica and giant cell arteritis
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	N/A. One of our trustees did disclose a conflict of interest as they have been consulting with the manufacturer for this process, so they have stepped back from any involvement at our end.
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Views have been gathered through comments shared in the charity's member survey, and from general comments and feedback from members during meetings and online.

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?	We are a patient organisation and our members are primarily those with the condition rather than carers. In our most recent member survey (2024), we found... Of 251 GCA patients who answered the question 'what was the biggest impact on your life following diagnosis?' • 17.1% (43 respondents) loss of confidence • 15.1% (38 respondents) mental health issues • 12.4% (31 respondents) not being able to do practical things around the home

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	In our most recent member survey with 258 respondents who have GCA, we found: 256 felt that campaigning to increase NHS access to non-steroidal medicines for GCA should be one of the charity's top three priorities Our members feel a lot of frustration that the main method of treatment is steroids. While they work well to control the condition and minimise the risk of sight loss, strokes and other complications, they come with serious sided effects, especially when used at high doses and or for a long period of time. There is frustration that alternative treatments like tocilizumab are not readily available to more people with the condition, and our members who have been treated with it are pleased with the results but very fearful about having it removed after 12 months and not being able to have it again if they relapse in future. Our membership are hungry to have access to more treatments.
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Not having to be reliant on steroids, more choice of treatments to find ones that work better for them and or have fewer side effects of steroids.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Not a disadvantage per se, but the uncertainty of whether this would be a treatment that effectively acted as a cure by taking their condition into long term remission, or whether it would relieve their symptoms while on treatment only to relapse once treatment is withdrawn.

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.	Those more affected by steroid side effects. Those that have been unsuccessful in tapering their steroid dosage without relapsing/recurring symptoms.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Equality and transparency of access. If this treatment is made available on the NHS, will access be universal or dependant on the local health board? Will it be proactively offered to those it could benefit or will it rely on the patient knowing to ask?

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Access to a wider choice of treatments is key to reducing the impact of long-term steroid use on individuals, as well as the associated cost to the NHS in treating and managing steroid induced side effects • Access to a wider choice of treatments will allow those struggling to manage the condition with steroids to find a medication that works for them, improving their quality of life and reducing their reliance on NHS services • • •

Thank you for your time.

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Single Technology Appraisal
Upadacitinib for treating giant cell arteritis [ID6299]
Patient Organisation Submission

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About you

1. Your name	
2. Name of organisation	Vasculitis UK
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Vasculitis UK support patients with all types of vasculitis and their families by providing peer to peer support, information and advice. We support research in vasculitis and grant research awards annually. Our funds come from donations and bequests. We have had some honorariums from industry (Vifor pharma) for patient participation in panels. We have around 1300 registered members, but we have more than 10,000 members in our online groups.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	By communicating with patients. We have two big online groups with around 7,000 patients each and we run a helpline 7 days per week. We also meet patients face to face in local support group meetings. For this appraisal we also asked relevant questions in our groups to gather feedback.

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?	Living with the disease is difficult and ongoing. It is a chronic unpredictable condition without cure that has unpredictable flares relapses and remissions. Diagnosis can take a long time during which people remain significantly unwell and at risk of further blood vessel/organ damage and complications. People often require help with all aspects of daily living, especially in an acute phase. Mobility can be impacted by significant aches and pains. People report debilitating fatigue (both physical and mental-brain fog), severe pain, headaches, jaw claudication, sleep disturbances, and side effects from long-term steroid use, including moon face, weight gain, osteopenia, diabetes, cataracts, glaucoma and adrenal insufficiency. Despite this, blood tests like CRP or ESR may appear "normal," leading to dismissal by healthcare providers and feelings of being unheard or invisible. The potential risk of vision loss or organ damage adds to increased anxiety and concern. The inability to sleep either due to pain, night sweats or side effects from medication can also add stress to the situation leading to frustration and further exhaustion. The realisation that life is never going to be the same is both alarming and distressing. One of our members said: <i>It's all so very difficult to cope with at times. I'm not the person I was.</i> The side effects of treatment can be as overwhelming as the disease itself. Steroids often cause insomnia, racing heart, blurred vision, and mental health issues, leaving people feeling as though they're living a nightmare. The burden of self-management, particularly tapering steroids without consistent support, adds stress and risk. A lady told us: <i>I was a very young and quite active 69-year-old. Having to let go of who I was and what I was able to do previously, took quite some getting used to when GCA and polymyalgia struck.</i> The Experience of Carers: The balance of power shifts from that of a partnership to that of carer, especially in the acute phase. It is difficult to plan as each day is different and hard to predict. Plans may have to be adjusted or cancelled at the last minute depending on how the cared for person is on the day. This can cause additional stress in the household, loss of friendships and breakdown of relationships. The concept of 'good and bad days' are difficult for some people to understand. Additional practical tasks may be needed in the home to support a loved one or physical help to attend medical appointments. They may also have to manage or support the patient to safely take their medication. Some people may become quite low in the mood, depressed and not their usual selves.

	There may be an inability for a person to take on their usual roles within the relationship or employment may be affected. There is lack of predictability to plan for the future and fear of relapses. Additional practical tasks may be needed in the home to support a loved one or physical help to attend medical appointments. Carers witness the decline in mobility, the emotional toll, and the pain their loved ones endure—often feeling helpless and some of them may become quite low in the mood, depressed and not their usual selves. Living with this condition is often described as a "living nightmare"—not just due to physical symptoms, but because of the emotional weight, social isolation, and lack of understanding. Both patients and carers need greater medical awareness, emotional support, and flexibility in treatment.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Feedback suggests that patients and carers have significant concerns about current treatments and the level of care provided for GCA and related conditions on the NHS. While steroids remain the primary treatment and can offer vital symptom relief, it can be long term with a range of serious, often distressing side effects. Many people feel the burden of managing these side effects—such as insomnia, weight gain, adrenal insufficiency, type 2 diabetes, osteopenia, psychological changes and vulnerability to infections—is placed entirely on them. Unwanted facial hair and hair thinning can also make the person feel embarrassed and uncomfortable in public. Tapering off steroids can be a challenge due to flares, and infection, requiring a rise in steroid doses again. This can feel like a backward step sometimes making the patient feel like a failure. One lady told us “It is a living nightmare. Horrific side effects from high dose steroids - insomnia, racing heart, blurry vision, the works.” A major issue is the lack of structured support for tapering steroids. Patients often feel pressured to reduce doses quickly, despite knowing from experience that this can cause painful flares and a setback in recovery. Some attempt self-management strategies, such as splitting doses throughout the day, which can help, but this is done without consistent medical guidance. There's a sense that the system pushes reduction as a goal, rather than focusing on sustainable, patient-centered care. Those who are immunosuppressed—especially when managing chemotherapy-like risks—report heightened vulnerability and inadequate safety nets or monitoring. The lack of flexibility and responsiveness in treatment pathways further fuels feelings of being unsupported and unsafe. Not all treatments are available to all patients, and some are given for a specific length of time and have to be stopped even if the patient responds well to the treatment.

8. Is there an unmet need for patients with this condition?	Yes, there is a lack of understanding around with some professionals regarding GCA, eg risk of visual loss but also the risk of other major blood vessels being involved such as the aorta. There is also a risk of circulatory complications further down the line after the acute phase, but this is not always recognized Whilst we understand steroids as a life saver it would be marvellous to have another medication to work along side it and reduce the length of time patients may need steroid therapy for, thereby reducing the risk of complications from steroids themselves. GCA is a rare condition, although it is the most common of the vasculitides, and the treatment options are limited. Therefore, we would say that there is an unmet need.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We don't have feedback from patients that have been on Upadacitinib, but GCA patients are very keen on having a new treatment option. Furthermore, the potential reduction to length of time taking steroids and the less additional medication needed to counteract any side effect to steroids would be a benefit.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As in all medications the risk of suffering from side effects is a disadvantage. Taking a medication that is new always causes some increased anxiety. Patients and carers believe that close monitoring is essential while taking this medication.

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.	All patients would benefit from a new treatment option, but patients with refractory GCA and patients with significant flare ups would certainly benefit more as current treatment are limited.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None I am aware of.

Other issues

13. Are there any other issues that you would like the committee to consider?	Early diagnosis and early and effective treatment are essential for good prognosis and better quality of life. GCA is a chronic disease, and patients commonly have flare ups. Every time you have a flare up more damage is done, sometimes irreversible and that affects the patient outcome.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Reduction in complications to steroid therapy. • Additional treatment option in a disease with limited choice of medications • Recognising the true impact of this disease on patients' lives

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Single Technology Appraisal
Upadacitinib for treating giant cell arteritis [ID6299]
Professional organisation submission

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 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	
2. Name of organisation	British Society for Rheumatology
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes
5a. Brief description of the organisation (including who funds it).	The British Society for Rheumatology is a professional body for rheumatology professionals – this submission has been completed by the Co-convenor of the British Society for Rheumatology vasculitis and polymyalgia rheumatica specialist interest group (SIG), Chair of the Group since May 2025.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	BSR has received the following funding from Abbvie over the past year: £80,000 - Conference sponsorship (2025). Abbvie would have been involved in the same even in 2024, but not invoiced in the last 12 months. £197,500 – Research Registers income (May 2024 - Apr 2025) including the Rheumatoid Arthritis Register. The BSR Journals haven't received any funding from Abbvie over the past 12 months. We have published research on Upadacitinib, but not as a BSR 'position'. The piece of work most likely to be relevant in this context would be BSR's axSpA guideline (https://doi.org/10.1093/rheumatology/keaf089)
5c. 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 induce sustained remission in those with refractory or relapsing disease despite first line treatment i.e., steroids, or are at high risk of steroid related side effects necessitating more rapid steroid taper that would typically be employed. In all groups, provide a meaningful steroid sparing effect. Refractory or relapsing disease would be associated with a higher cumulative steroid burden and associated risk of toxicity and morbidity.
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.)	Sustained or complete sustained remission – absence of symptoms consistent with active GCA, as well as biochemical improvement (normalisation of inflammatory markers) and no progression of radiographic appearances (e.g., ultrasound, PET-CT imaging).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – there is currently only one commissioned steroid sparing agent for GCA, tocilizumab (TA518). Data from the original GIACATA would suggest that approximately only half of patients may respond favourably to tocilizumab, meaning there is no good treatment options beyond this apart from further steroids, which are toxic in the long term. For those that do respond favourably to tocilizumab, NICE has currently imposed a 12-month limit on use, with no option for retreatment in the event of subsequent relapse on stopping. From observational data we know approximately half of patients will relapse again after Tocilizumab is stopped (Quick et al. Rheumatology (Oxford). 2024 Dec 1;63(12):3407-3414. doi: 10.1093/rheumatology/kead604 . PMID: 37952183).

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	First line treatment is steroids, typically tapered over the course of 12-18 months depending on the regimen used. For those with relapsing disease most clinicians would consider introducing either Methotrexate or Tocilizumab (TA518).

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	British Society for Rheumatology guidelines – Mackie SL et al. British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis, <i>Rheumatology</i> , Volume 59, Issue 3, March 2020, Pages e1–e23, https://doi.org/10.1093/rheumatology/kez672
9b. 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.)	There is wide variation in pathways for GCA. From the GIRFT report, 34% of hospitals in England did not have any formal clinical pathway for assessing GCA. Standards of care have been proposed (Coath FL et al. <i>Rheumatology</i> (Oxford). 2023 Sep 1;62(9):3075-3083. doi: 10.1093/rheumatology/kead025.PMID: 36692142).
9c. What impact would the technology have on the current pathway of care?	It is important to emphasise that relapse rates in GCA are high as steroids are tapered, 50-80%, and so treatments other than steroids are very much needed. Methotrexate does not have marketing authorisation for GCA as it is a generic drug, but there is meta-analysis data for use and nonetheless widely used. As above, tocilizumab use is limited to 12 months, with no option for retreatment in those who had a good response and relapse once stopped. From observational data we know approximately half of patients will relapse again after tocilizumab is stopped (Quick et al. <i>Rheumatology</i> (Oxford). 2024 Dec 1;63(12):3407-3414. doi: 10.1093/rheumatology/kead604 . PMID: 37952183). For these patients, again there are currently no good treatment options except steroids, which are very toxic in the long term.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Clinicians may be caught between using a JAK inhibitor, which may have thromboembolic and infection risk in the elderly (the target demographic), and tocilizumab (TA518), which can be difficult to tolerate. It would be useful to have guidance on which of the two drugs it might be better to use first (on grounds other than cost). It would also give clinicians the chance to consider what happens to people after the first 12 months of tocilizumab. It is logically incoherent to consider a novel drug for these patients but at the same time, not to allow re-treatment with a (likely cheaper) drug that may have worked very well for them previously.
10a. How does healthcare resource use differ between the technology and current care?	Beyond an additional appointment for education on Upadacitinib, if patients can be brought into remission and reduce their steroid exposure, overall healthcare resource use should be reduced e.g., less clinic appointments and investigations for relapses and consequences of cumulative steroid use.
10b. In what clinical setting should the technology be	Secondary care and specialist clinics.

used? (For example, primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No extra investment envisaged. Upadacitinib is already used for other rheumatological conditions, so most centres will already have adequate training, specialist nurse support and experience with this drug.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – as above, for the patient groups in whom Upadacitinib is likely to be used (refractory/relapsing), there are limited treatment options.
11a. Do you expect the technology to increase length of life more than current care?	Yes – in that if a meaningful steroid sparing effect is achieved, we may see less steroid toxicity, which itself can be life limiting e.g., cardiovascular disease, diabetes, osteoporosis etc.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes – both in terms of clinical remission from the disease itself and associated steroid sparing benefits. Current UK standard of care is not sufficient.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes – epidemiological data shows the incidence of GCA rises steadily in those over 50 years of age, peaking in the ninth decade with an annual incidence (95% CI) of 190.4 (144.9 to 245.6) by the 1990 ACR criteria, and 203.3 (156.2 to 260.1) by the 2022 ACR/EULAR criteria. Mukhtyar CB et al. Ann Rheum Dis. 2023 Oct;82(10):1341-1347. doi: 10.1136/ard-2023-224191. Epub 2023 Jun 30. PMID: 37399329. Of those with GCA it is important to emphasise that relapse rates can be 50-80%, and so treatments other than steroids are very much needed.

The use of the technology

13. Will the technology be easier or more difficult to	No more difficult than current care. Upadacitinib is already used for other rheumatological conditions, so most centres will already have adequate training, specialist nurse support and experience with this drug. Beyond an

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.)	additional appointment for education on Upadacitinib, if patients can be brought into remission and reduce their steroid exposure, overall healthcare resource use should be reduced e.g., less clinic appointments and investigations for dealing with relapses and consequences of cumulative steroid use.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There should be rules. We would recommend the initial diagnosis have objective basis (i.e., imaging or biopsy), and then relapse should also be objectively shown wherever possible (i.e., imaging, blood results etc.).
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?	Yes - the reduction of corticosteroid use will most definitely improve Health-related quality of life (HRQOL), but that will be difficult to quantify.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and	Yes – it is targeting a completely different pathway from drugs we currently have available, in a disease where we know approximately 50% of patients do not respond to the only current commissioned drug tocilizumab (GIACTA trial).

how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes - Of those with GCA it is important to emphasise that relapse rates can be 50-80%, and so treatments other than steroids are very much needed.
17. 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 phase 3 study for Upadacitinib (Blockmans D et al. SELECT-GCA Study Group. A Phase 3 Trial of Upadacitinib for Giant-Cell Arteritis. N Engl J Med. 2025 Apr 2. doi: 10.1056/NEJMoa2413449. PMID: 40174237) had an acceptable side effect profile, with the incidence of serious infections higher in the placebo (steroid only) group than with Upadacitinib. A higher incidence of herpes zoster was observed, which is a known class effect of JAK inhibitors, and could be mitigated for with vaccination. There have been prior warnings about venous thromboembolism risk with JAK inhibition, but again, no significant difference was observed between the placebo and Upadacitinib groups. Overall given prior warnings from the Medicines and Healthcare products Regulatory Agency, the safety profile in SELECT-GCA was relatively reassuring (https://www.gov.uk/drug-safety-update/janus-kinase-jak-inhibitors-new-measures-to-reduce-risks-of-major-cardiovascular-events-malignancy-venous-thromboembolism-serious-infections-and-increased-mortality (last accessed 06/06/2025)).

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The only study of Upadacitinib in GCA is the SELECT-GCA trial (Blockmans D et al. SELECT-GCA Study Group. A Phase 3 Trial of Upadacitinib for Giant-Cell Arteritis. N Engl J Med. 2025 Apr 2. doi: 10.1056/NEJMoa2413449. PMID: 40174237). This was a 52-week randomised controlled trial whereby patients were randomised to either placebo (52-week steroid taper), or one of two Upadacitinib arms, 7.5 mg or 15 mg, both with a 26-week steroid taper. The study met its primary endpoint, with sustained remission at week 52 was observed in a significantly higher percentage of patients who received Upadacitinib at a dose of 15 mg than in those who received placebo

	(46.4% vs. 29.0%; P=0.002). The 7.5-mg dose of Upadacitinib did not lead to a significantly higher percentage of patients with a sustained remission than placebo (41.1% vs. 29.0%).
18a. If not, how could the results be extrapolated to the UK setting?	- The trial included both new and relapsing patients, approximately 70% to 30% split respectively across all the three randomised groups. This would differ from current UK practice in that Upadacitinib is likely to be positioned for relapsing or refractory groups only. There is no sub-group analysis of the relapsing patients, the numbers may be too small for this. - The study methodology also excluded patients who had previously experienced a disease flare whilst on IL6 inhibition. Some patients are noted to have prior exposure IL6 inhibition (table 1); however, these were small numbers and so not suitable for sub-group analysis. We therefore have no data to guide where to place Upadacitinib in the treatment pathway i.e., before/after tocilizumab.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	- The study met its primary endpoint, with sustained remission at week 52 was observed in a significantly higher percentage of patients who received Upadacitinib at a dose of 15 mg than in those who received placebo (46.4% vs. 29.0%; P=0.002). The 7.5-mg dose of Upadacitinib did not lead to a significantly higher percentage of patients with a sustained remission than placebo (41.1% vs. 29.0%). - Also of importance, the total cumulative exposure to steroids over the course of the study was significantly lower in the Upadacitinib 15 mg arm than with placebo (median exposure, 1615 mg vs. 2882 mg; P<0.001).
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The total cumulative exposure to steroids over the course of the study was significantly lower in the Upadacitinib arm than with placebo. Although there was no significant difference in adverse effects, beyond 52 weeks I would eventually expect see more steroid related adverse events in the steroid only placebo group. The study duration is not long enough to demonstrate this here, but we can extrapolate from other studies on the effects of long terms steroid risks. For patients who have experienced steroid toxicity or are at high risk of future steroid toxicity, the technology would therefore be expected to be more cost-effective in this patient group. For example, patients who have diabetes, fracture, glaucoma, impaired healing, significant weight gain, or significant neuropsychiatric adverse effects. (Lyne SA et al. Consensus of the definitions of the OMERACT glucocorticoid impact core domain set for people with rheumatic and musculoskeletal diseases. Semin Arthritis Rheum. 2024 Feb; 64:152338. doi: 10.1016/j.semarthrit.2023.152338. Epub 2023 Dec 16. PMID: 38134623).

	The study also looked at patient-reported outcomes including scores on the Functional Assessment of Chronic Illness Therapy – Fatigue, the Physical Component Summary of the 36-item Short-Form Health Survey, and the Treatment Satisfaction Questionnaire for Medication patient global satisfaction subscale. This does not explicitly explore. However, both the limited study duration of 52-weeks and modes of assessment chosen are likely to underplay the negative effects of long-term steroid burden in GCA patients. The adverse effects of long-term glucocorticoid treatment should reflect all the core domains specified by OMERACT ((Lyne SA et al. Consensus of the definitions of the OMERACT glucocorticoid impact core domain set for people with rheumatic and musculoskeletal diseases. Semin Arthritis Rheum. 2024 Feb; 64:152338. doi: 10.1016/j.semarthrit.2023.152338. Epub 2023 Dec 16. PMID: 38134623). These include infection, bone fragility, mood disturbance, hypertension, diabetes, weight, and fatigue. Patients with absolute contraindications to steroids - psychosis for example - should also be included when assessing outcomes. Consideration should also be given to capturing the steroid dose required to control disease activity, cumulative steroid dose, impact of steroids on patients' lives. It is essential to consider the mental-health sequelae of the disease itself as well as the steroid therapy (Robson JC et al. Patient perceptions of health-related quality of life in giant cell arteritis: international development of a disease-specific patient-reported outcome measure. Rheumatology (Oxford). 2021 Oct 2;60(10):4671-4680. doi: 10.1093/rheumatology/keab076. PMID: 33528002; PMCID: PMC8487303).
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to our knowledge.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology	TA512 appears to relate to 'Tivozanib for treating advanced renal cell carcinoma', I'm assuming this was an error? TA518 'Tocilizumab for treating giant cell arteritis': From observational data we know approximately half of patients will relapse again after tocilizumab is stopped (Quick et al. Rheumatology (Oxford). 2024 Dec 1;63(12):3407-3414. doi: 10.1093/rheumatology/kead604. PMID:

appraisal guidance [TA512]?	37952183). For these patients, again there are currently no good treatment options except steroids, which are very toxic in the long term.
21. How do data on real-world experience compare with the trial data?	We have not been able to use this treatment yet in GCA, so unable to comment.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Older people are disproportionately affected by this condition, almost exclusively affecting adults over the age of 50 year, with increasing incidence with each subsequent decade. It more commonly occurs in women than men. Risks of the disease itself (e.g., risk of ischaemic complications such as permanent sight loss, which could lead to functional deficit and social isolation), and cumulative steroid burden are compounded by the effects of aging. Moreover, if the model set out for tocilizumab commissioning was followed (TA518), with implementation via specialised centre approval, this would disadvantage patients living in remote and rural locations. Older people and those with disabilities are over-represented in rural locations, whereas specialised centres tend to be based at urban university hospitals with a younger population. Therefore, requirement for specialised centre approval as is currently the case for tocilizumab could unfairly disadvantage older individuals and those with disabilities. (Quick V et al. TOC STOP 2022 Investigators. Relapse after cessation of weekly tocilizumab for giant cell arteritis: a multicentre service evaluation in England. Rheumatology (Oxford). 2024 Dec 1;63(12):3407-3414. doi: 10.1093/rheumatology/kead604. PMID: 37952183.)
22b. Consider whether these issues are different from issues with current care and why.	NA

Topic-specific questions

23 Are you aware of any evidence of tocilizumab being used outside of TA518 recommendations?	Yes, outside of England: • Colleagues in Scotland are allowed to use tocilizumab beyond 1 year at the clinicians discretion according to guidance laid out by the Scottish Medicines Consortium (SMC) (Conway at al., Benchmarking tocilizumab use for giant cell arteritis, <i>Rheumatology Advances in Practice</i>, Volume 6, Issue 2, 2022, rkac037, https://doi.org/10.1093/rap/rkac037). • EULAR - recommend adjunctive therapy such as Tocilizumab in patients who have already developed or have either an increased risk of developing GC-related side effects or complications, such as osteoporosis, diabetes, cardiovascular disease or glaucoma, or for relapsing patients irrespective of other risk factors. There is no specification on how long to use, only to consider tapering once patients achieve remission. (Hellmich B, <i>et al</i> 2018 Update of the EULAR recommendations for the management of large vessel vasculitis <i>Annals of the Rheumatic Diseases</i> 2020;79:19-30.) • ACR – recommends offering tocilizumab to all patients with GCA at initial diagnosis. Again there is no restriction on duration of treatment specified (Maz M et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. <i>Arthritis Rheumatol.</i> 2021 Aug;73(8):1349-1365. doi: 10.1002/art.41774. Epub 2021 Jul 8. PMID: 34235884)

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• This technology appraisal is very welcome in this area of significant unmet need, with only one currently available steroid sparing agent via TA518 (tocilizumab), which has a time-limit of 12 months. • The phase 3 trial of Upadacitinib (SELECT-GCA) appears to show statistically significant efficacy in achieving sustained remission compared to placebo (steroids alone). • There is a significant reduction in steroid use in the Upadacitinib arm. The potential clinical and economic gains from this will not be observed from a 52-week trial but should be strongly considered when reviewing this technology appraisal. • The safety profile of Upadacitinib in the trial was satisfactory when compared to placebo, especially reassuring in this older patient cohort. • Why is NICE considering only Upadacitinib and not concurrently reviewing the appropriateness of the current tocilizumab guidance TA518. It is logically incoherent to consider a novel drug for these patients, but at the same time, not to allow treatment beyond 12 months/re-treatment with a (likely cheaper) drug that may have worked very well for them previously.

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Single Technology Appraisal

Upadacitinib for treating giant cell arteritis [ID6299]

Clinical expert statement

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Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

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Part 1: Treating giant cell arteritis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Sarah L Mackie
2. Name of organisation	University of Leeds; Leeds Teaching Hospitals NHS Trust
3. Job title or position	Associate Professor in Vascular Rheumatology, University of Leeds Honorary Consultant Rheumatologist, Leeds Teaching Hospitals NHS 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 giant cell arteritis? ☒ A specialist in the clinical evidence base for giant cell arteritis 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 did not submit one, I do not 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
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links with the tobacco industry to declare.
8. What is the main aim of treatment for giant cell arteritis?	To prevent disability (physical and mental health-related quality of life).

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	In treating patients with GCA, we aim to restore quality of life by alleviating the signs and symptoms of the disease, while minimising any short- or long-term adverse impact of treatment on quality of life.
9. 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)	Remission: not having any symptoms or signs of active GCA.
10. In your view, is there an unmet need for patients and healthcare professionals in giant cell arteritis?	Yes, there is a real unmet need, given the limited treatment options currently available for GCA. A short summary of the various subgroups as defined in the scope document: • <i>Newly-diagnosed GCA</i>: no current treatment other than high-dose glucocorticoids; high-dose glucocorticoids are very toxic, and so dose tapering (gradual treatment withdrawal) is needed, with the expectation that treatment withdrawal will cause GCA relapse in 50%. Each relapse carries a risk of blindness/stroke. • <i>Relapsing GCA</i>: these patients may currently receive tocilizumab (TCZ) but only for one year. Apart from the known risks of TCZ therapy, using TCZ has some practical challenges: (1) it is not possible to reliably tell which patients are responding to TCZ or not, because the glucocorticoid dose is tapered down during TCZ treatment, (2) lack of ability to use the blood tests (CRP/ESR) that assist clinicians in confirming/refuting GCA relapse (because CRP/ESR are suppressed by tocilizumab), which increases clinical uncertainty and may necessitate advanced vascular imaging or “just in case” escalation of the glucocorticoid dose if the patient should develop new symptoms, even if non-specific. • <i>GCA patients with previous glucocorticoid toxicity, or pre-existing conditions likely to be exacerbated by glucocorticoids</i>: are high risk of serious medical complications with the currently available glucocorticoid treatment, and TCZ is not available to them unless they are relapsing/refractory and approved by the regional MDT.

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

4 of

	• <i>GCA patients who have had up to twelve months of TCZ:</i> By one year after stopping TCZ, one-third of patients have a further relapse, and by two years after stopping, half have had a further relapse (Quick et al., 2024). Other than glucocorticoids, which are very toxic, there are currently no treatment options for these patients as they are not allowed any further courses of TCZ under NICE TA518. • <i>GCA patients for whom TCZ is unsuitable:</i> no current treatment other than glucocorticoids, which are very toxic; or off-label csDMARDs such as methotrexate, which have unclear efficacy and a known toxicity risk profile in older people.
11. How is giant cell arteritis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	Brief answers: - Yes, clinical guidelines are used: in the NHS, we follow the British Society for Rheumatology GCA guidelines. - Yes, the pathway of care is well-defined for glucocorticoids and tocilizumab. Although the pathway is the same in all NHS Trusts, the actual rate of tocilizumab prescribing is higher in specialist centres than outside specialist centres. Furthermore there is a difference of opinion as to whether it is worth using csDMARD drugs such as methotrexate, due to the relatively weak evidence for efficacy in GCA, and their toxicity profile in older people. - Initially, clinicians would likely use this new technology with caution and in a few patients only. As time goes on and experience builds, having this technology as a treatment option would enable a more individualised approach to patient treatment. The competition in the market would drive further progress in this disease in various ways (see below). Please find below further details along with the reasoning and evidence to explain my answers.

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

5 of

	<i>Guidelines, and whether they are followed</i> In the NHS, we tend to follow the British Society for Rheumatology guidelines, that were published in 2020. There are also some other relevant guidelines, such as the guidelines for osteoporosis prevention/treatment and adrenal insufficiency management. The references to these are all included at the end of this section. These guidelines are well-accepted amongst rheumatologists. There is some variation in the NHS as to how the adverse effects of glucocorticoids are monitored. In primary care, glucocorticoids (“corticosteroids”) tend to be viewed differently as they are more often given as short courses for acute conditions such as asthma exacerbation, idiopathic sudden sensorineural hearing loss, etc. In contrast, GCA treatment starts out as high-dose and then becomes long-term, producing a different toxicity profile to the profile GPs are more familiar with from short-term treatment. GPs would tend to consult the NICE Clinical Knowledge Summaries “CKS” website, produced by Clarity Informatics Limited. In patients taking corticosteroids, “NICE CKS” advises checking weight, blood pressure, blood tests for diabetes, triglycerides and potassium, eye tests for glaucoma or cataract, patient education and lifestyle advice, and ongoing monitoring for adverse effects (CKS provides a list of about 50 possible adverse effects to be aware of). In practice, this monitoring happens inconsistently; the monitoring work is variably divided between primary and secondary care; our patient and public involvement work has repeatedly suggested that quite often, most of recommended monitoring for glucocorticoid toxicity does not seem to happen at all; this work is medically complex and distributed across organisational boundaries, specialities and services. This difficulty in comprehensive monitoring is a patient safety risk but has been difficult to address in small-scale quality improvement projects.

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

6 of

	<i>Early treatment: a well-defined pathway for newly-diagnosed GCA patients</i> Using high-dose glucocorticoid (corticosteroid, “steroid”) therapy, we aim to achieve initial remission as rapidly as possible. BSR guidelines (Mackie et al., 2020) suggest using high-dose intravenous glucocorticoids for GCA patients with threatened visual loss; most other patients receive high-dose oral prednisolone as in practice it can be quicker to give an oral medication than to admit the patient to hospital for IV steroids. If a high enough glucocorticoid dose is given, this usually achieves remission. If initial remission does not occur, we call this “refractory GCA”. Refractory GCA is uncommon, perhaps up to 5% of patients in total; patients with refractory GCA are at high risk of sudden-onset early complications such as irreversible blindness or stroke. Early treatment is well defined and generally accepted by the medical community. High-dose glucocorticoid therapy causes adverse effects in almost all patients with GCA. Those with immediate impact on patients commonly include: inability to sleep, hunger, anxiety, agitation, tremor, irritability, aggression or frank psychosis. Other “invisible” impacts, such as diabetes or osteoporosis/fragility fracture, tend to manifest later, but clinicians worry about the long-term harms of glucocorticoids to patient health. Co-prescription of medication to protect stomach and bone is standard. Guidance for monitoring and mitigating the risk of future fragility fracture, which can be devastating if it occurs, include the guidelines on prevention of glucocorticoid-induced osteoporosis from the UK National Osteoporosis Guideline Group, NOGG (Gregson et al., 2022), which recommend referral to an osteoporosis specialist for any patient who will receive over 7.5mg prednisolone daily for 3 months or more, and empiric oral bisphosphonate therapy if there will be any delay in this. A few patients cannot take high-dose glucocorticoids at all. These include those who have had glucocorticoids prescribed previously for other conditions, such as asthma exacerbation or polymyalgia rheumatica, and have developed severe adverse effects, for example psychosis or suicidality.

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

7 of

	<i>After remission achieved: we taper glucocorticoids as fast as we dare</i> After remission is achieved, using high-dose glucocorticoid therapy, we need taper the glucocorticoid dose as quickly as possible (“as fast as we dare”) to avoid doing harm to patient health. A typical “as fast as we dare” means the dose taper described in the BSR guidelines (which lasts about 18 months, providing no relapse occurs). But “the taper” is not really, as is often presented, a programme of treatment; it is actually a process of slow treatment withdrawal, necessitated by the harm that glucocorticoids do. This taper regimen is relatively standardised, with some minor modifications for patient-related (eg previous/current glucocorticoid toxicity or pre-existing conditions likely to be worsened by glucocorticoid therapy) and for disease-related factors (eg pattern of vascular involvement). In many other countries, such as USA and Australia, newly-diagnosed patients are treated with TCZ alongside glucocorticoids to prevent relapse. In the NHS TCZ can only be given to GCA patients who have relapsed already. The concern is that, since blindness/stroke can happen at any relapse, we run the risk of leaving it too late to prevent these devastating outcomes. Sometimes other medications (eg methotrexate) are given for relapse prevention, but the evidence base for efficacy is weak and the tolerability profile of methotrexate can make it difficult in older patients. <i>Managing relapses</i> GCA is a chronic disease: research studies have shown persistent inflammation of GCA temporal artery biopsies, even in treated patients in apparent clinical and laboratory remission. Relapse during glucocorticoid taper happens in about 50% of patients with GCA, and this necessitates glucocorticoid dose escalation. Anecdotally, the adverse effects of a second period of time on high-dose glucocorticoids seem to have a far worse impact on the patient than the initial treatment, even though the dose was the same as was used before. This is reflected in clinical opinion and epidemiological evidence that the risks of glucocorticoid therapy are a function of both current dose and the cumulative

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

8 of

	dose (ie the persistent adverse effects of all the glucocorticoids that have been taken previously, combines with the effect of the dose that is being taken now). During the glucocorticoid taper, patients need frequent follow-up consultations (every 3-6 months), due to a 50% risk of GCA relapse at some point during the taper. It is very difficult to know at the start which patients are going to relapse, and if so, at what glucocorticoid dose. Clinicians advise patients to seek medical advice promptly if they should experience symptoms to suggest a relapse of GCA. Blood tests ("inflammatory markers"), such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), can be useful, either for early detection of relapse (when symptoms can be very non-specific e.g. tiredness, loss of appetite or body aching) or for helping to confirm relapse (when symptoms and signs point more clearly to GCA). An important alternative explanation for return of non-specific symptoms during/after glucocorticoid taper is glucocorticoid withdrawal symptoms (described in NICE Guideline NG243); glucocorticoid withdrawal symptoms can be hard to disentangle from true GCA relapse, especially as patients tapering steroids are often still experiencing persistent glucocorticoid toxicity which may itself produce many symptoms including fatigue, muscle weakness, headaches etc. Disentangling relapse, glucocorticoid withdrawal syndrome and persistent glucocorticoid toxicity generally requires specialist expertise and this is why GCA must be managed under specialist care, typically rheumatology. Continuity of care and regular follow-up consultations are important to keep patients safe. Every rheumatology department arranges follow-up care slightly differently, in line with the local context, but the principles of management are the same everywhere. <i>Methotrexate and other conventional synthetic disease modifying antirheumatic drugs (csDMARDs):</i> Although methotrexate is conditionally recommended in the 2020 BSR guidelines (Mackie et al., 2020), in real-world practice, it is often not tolerated well by older patients, and adverse effects often outweigh the benefits it might bring to GCA disease control; practice has evolved since the 2020 guidelines, and now the benefits of methotrexate in GCA are considered by many

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

9 of

	rheumatologists as somewhat marginal. Leflunomide, a different csDMARD, is also sometimes given off-label for GCA, but there is no trial-based evidence of its efficacy in GCA. csDMARDs require fortnightly blood test monitoring initially, and the risks of adverse effects of methotrexate are higher in older patients and those with chronic renal impairment; methotrexate can be fatal if incorrectly taken as a daily dose rather than weekly as prescribed (Mackie and Hill, 2025). There is some regional variation as to what proportion of patients with GCA are prescribed csDMARD therapy at all. As a rule, csDMARDs tend to be given when there is concern about actual or potential glucocorticoid toxicity and no other treatment option. <i>Tocilizumab (TCZ):</i> TCZ, as a treatment for GCA licensed since 2017 and now available as biosimilar, is now well-established globally as a first-line treatment alongside high-dose glucocorticoids for newly-diagnosed GCA (see American College of Rheumatology/Vasculitis Foundation guidelines, Maz et al., 2021). However, under NICE TA518, TCZ is reserved for refractory or relapsing GCA; only one year of uninterrupted treatment is allowed in any patient's lifetime, and it must be approved via a regional multidisciplinary team located in a specialist centre. In European countries (eg Sweden, Ireland, Spain), TCZ is customarily given for GCA for one year at full dose, 162mg weekly by subcutaneous self-injection (s/c), then one year at half-dose (162mg fortnightly s/c), then spaced out and stopped if no relapse occurs (two to three years' TCZ treatment in all). This is sometimes referred to as "tapering" TCZ. Some UK rheumatologists "taper" the final three months of the permitted one year of TCZ; although this was not recommended in NICE TA518, there is some evidence that spacing out or "tapering" TCZ doses can prolong treatment response compared to "coming to a hard stop" (Quick et al., 2025). However, TCZ therapy carries its own risks, not all of which are eliminated by blood monitoring (typically blood tests are needed 1, 3, 6 and 9 months of treatment).

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

10 of

	There are specific implications for using TCZ in the context of current GCA care pathways, that may have reduced NHS clinicians' willingness to prescribe it. Because TCZ directly acts on IL-6 receptor signalling, it interferes with the ability of the liver to produce an acute phase response. This means that the "inflammatory marker" blood tests we use to monitor GCA will give misleadingly normal results, even if there is a true GCA relapse. This makes it extremely difficult to know for sure whether any new symptoms experienced by patients are true GCA relapse or not. Clinicians tend to respond to this uncertainty either by increasing the glucocorticoid dose "just in case", or by ordering specialised vascular imaging tests such as PET-CT, magnetic resonance angiography, or temporal artery ultrasound scans that in the NHS are mostly done by consultant rheumatologists. In the meantime, many rheumatologists encourage patients taking TCZ to taper glucocorticoids down quickly, aiming to stop glucocorticoids entirely, but this rapid taper-to-stop can precipitate GCA relapse in some patients; it is not necessarily that TCZ isn't working at all, but that sometimes a small dose of glucocorticoid is still needed alongside in order to maintain sustained remission. It's therefore not possible to reliably identify TCZ responders/non-responders because of the necessity to taper down glucocorticoids during TCZ treatment. Another consequence of the suppression of ESR/CRP by TCZ is that, like high-dose glucocorticoids, TCZ can increase the risk of gastrointestinal perforation (from diverticulitis) while masking clinical signs of sepsis. This can be very dangerous. Previous history of complicated diverticulitis is an example of a comorbidity that would make a patient unsuitable for TCZ therapy. There is substantial national variation in TCZ prescribing rates. We noticed in the "TOC STOP" study (Quick et al., 2024) that certain Trusts have much higher rates of prescribing than others. This did not appear explainable by demographic or variation in GCA incidence/severity and we wondered if it was due to disparities in ease of access to the regional specialist centre multidisciplinary teams (MDTs), which need to approve TCZ for each individual patient.

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

11 of

	Another possible reason for under-prescribing of TCZ in the NHS is the current severe pressure on rheumatology services: so the difficulty in monitoring GCA patients on TCZ for relapse, when blood tests (ESR/CRP) cannot be used as they normally would, is particularly problematic in Trusts where there is limited access to specialist vascular imaging (ultrasound by highly-trained consultant rheumatologists, PET-CT, MRI). <i>Potential impact of the technology (upadacitinib) on the current pathway of care.</i> UPA has been shown to be efficacious in the pivotal trial SELECT-GCA, without any new safety signals of concern. UPA could be given in combination with glucocorticoids, or alone. UPA would not be combined with TCZ. The technology (upadacitinib, “UPA”) has some advantages in this patient group in comparison to TCZ: • UPA is given as a once daily dose (can be stopped and restarted readily in the case of intercurrent infection) • UPA is a tablet, compared to TCZ which is given as a self-administered weekly injection (better for patients who want or need to travel) • UPA does not completely suppress CRP/ESR, as TCZ does, and therefore it is easier to detect GCA relapse without use of scarce resource (vascular imaging – consultant rheumatologist time doing ultrasound, or use of PET-CT or MRI scanner). From what we know about pharmacodynamics and mechanism of action, it is possible that UPA may start working more quickly than TCZ, enabling glucocorticoids to be tapered sooner; but this is not certain. No comparative effectiveness studies of TCZ vs UPA have been done yet in GCA, and it is difficult to make an efficacy comparison between the two pivotal trials as these two trials differ in some important ways, e.g. eligibility criteria, available treatment alternatives at the time the trials were done, and outcomes.

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

12 of

	Some of the other risks and downsides, such as need for blood monitoring and risk of infections including shingles reactivation, apply to all treatments for GCA (TCZ, UPA and glucocorticoids). There are safety concerns with the JAK inhibitor class that has led to a “black box warning”; clinicians are aware of this and the safety considerations will be built into any treatment pathway. These risks should be considered in the context of the risks of other treatment options (glucocorticoids, TCZ) and the potentially sight-threatening nature of the disease itself. <i>Speculations about how UPA may change the treatment pathway</i> Based on my own mapping of the current GCA treatment landscape, and my observations of the impact of the approval of TCZ in UK and other countries, I would predict that introducing upadacitinib (“UPA”) as an option for the treatment of GCA in the NHS might have short-, medium- and long-term consequences. The next three paragraphs are highly speculative and represent my own personal view. <i>Short term (1-3 years):</i> safety will be the main driver of treatment decisions, as it was in the early days of using TCZ for GCA. Rheumatologists, familiar with UPA from its established use in other indications, will use UPA cautiously, probably at first reserving it only for relapsing, post-TCZ GCA patients under 65 years and without history of malignancy, atherosclerotic cardiovascular disease, or history of heavy smoking. Until clinicians become comfortable with using UPA for GCA, they will likely choose TCZ in preference if it is available; but until TA518 is revised, there will be many relapsing GCA patients who will not be able to have TCZ, and will instead be considered for UPA. Patients will be counselled carefully and clinicians prescribing UPA will initially discuss all cases with expert colleagues; either informally, or formally at the regional MDTs that are already in place for TCZ initiation decisions and provide documentation of a positive opinion. These TCZ MDTs will likely be renamed TCZ/UPA MDTs at first, or simply GCA MDTs. Treatment choices in GCA will be a hot topic at rheumatology conferences and educational meetings.

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

13 of

	<i>Medium term (3-5 years):</i> post-marketing safety surveillance data on the safety of UPA in GCA will accumulate, and be shared. Experience in using UPA in GCA amongst the “early adopters”, plus the accumulating safety data, will determine how UPA is implemented in the sequence of treatments for GCA. A major revision to the British Society for Rheumatology guideline on GCA will be published (and American and European guidelines will also be revised), and “box and arrow” infographics will summarise “expert best practice” in selecting treatment options for GCA. There will be an up-skilling of the workforce in GCA, starting with education programmes for clinical nurse specialists. Patients with GCA will benefit from a more holistic approach to their care, and will change from the current “battleground” of glucocorticoid dosing decisions to a more collaborative, patient-centred discussion comparing the different treatment options. At this stage, TCZ will still likely be preferred by most UK rheumatologists, as they will be more familiar with using it in GCA; if NICE TA518 is revised to allow repeat/longer TCZ treatment, use of TCZ may increase faster than use of UPA. Use of csDMARD such as methotrexate will decline, unless shown to be efficacious in high-quality trials. More widespread use of effective treatments for GCA, that are safer than steroids, will begin to improve clinical outcomes of patients with GCA. Other companies will develop competitor drugs for GCA, further driving down costs. UPA will become available as cheaper generic and competition in the TCZ biosimilar market will make TCZ become ever cheaper. At this point, NIHR HTA will commission a “head to head” trial of two alternative standards of care: UPA compared to TCZ for relapsing GCA, both given alongside a rapid glucocorticoid taper. <i>Long term (beyond 5 years):</i> the place of TCZ and UPA, or their biosimilar/generic equivalents, in the GCA treatment pathway will become so well-embedded into practice, and so clearly articulated in patient-facing shared-decision making tools, so that it is not much discussed anymore at conferences. GCA patient outcomes will continue to improve. Rheumatologists will not need to spend time discussing how to improve clinical pathways to keep their GCA patients safe while taking high-dose, long-term glucocorticoid therapy, because

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

14 of

prolonged high-dose glucocorticoid treatment in GCA will become much less common. The rate of late fragility fractures and other late glucocorticoid-related toxicities in GCA patients will decrease. Research will continue, more new products will be developed, and perhaps NICE will be asked to consider another new technology for treating/monitoring GCA that has the potential to change the treatment pathway yet again.

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Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

16 of

	multicentre evaluation. Rheumatology (Oxford). 2025 Aug 26;keaf450. doi: 10.1093/rheumatology/keaf450. Epub ahead of print. PMID: 40857555.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	1. In current care: - glucocorticoids are cheap, but monitoring for toxicity requires considerable healthcare resource use, and their complications (sepsis, fracture, diabetes etc) can be very costly. - TCZ is expensive, and suppression of ESR/CRP may lead to delayed recognition of sepsis and inability to detect GCA relapse without repeated advanced vascular imaging tests, that incur high healthcare costs and burdens to patients. But use of TCZ enables less use of glucocorticoids, thereby reducing glucocorticoid-related healthcare resource use. - The technology under consideration, UPA, is also expensive, but UPA does not suppress ESR/CRP as profoundly as TCZ, so accurate detection of GCA relapse is easier. Use of UPA also enables less use of glucocorticoids, thereby reducing glucocorticoid-related healthcare resource use. The known safety profile of JAK inhibitor drugs, including UPA, is likely to mean that in practice it will be prescribed very cautiously in many patients (eg over-65s) until experience accumulates in this disease. 2. The technology, UPA, will be prescribed and monitored in secondary care, by rheumatologists. 3. The drug, UPA, is already prescribed in everyday practice in many other indications across rheumatology, but its use in GCA may benefit from formal/informal professional networks and educational initiatives. The rheumatology community is likely to take a lead role in developing these.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	1. It is unlikely that the technology will increase length of life across the entire population of GCA patients.

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

17 of

- Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	2. The patient-reported outcome data in SELECT-GCA showed that patients taking UPA with a 26-week glucocorticoid taper had better outcomes than those taking PBO with a 52-week glucocorticoid taper: both SF-36 PCS (SF-36 physical component summary score, a summary score of physical health-related quality of life), and in relation to FACIT-F, a well-established patient-reported measure of fatigue. The combined burden of glucocorticoid therapy and partially-treated GCA typically causes significant physical disability and fatigue in my patients. Based on this trial data, I would expect this technology to improve health-related quality of life compared to current care.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The two sub-groups, within the “general GCA population” who would benefit most from the technology, are: <i>GCA patients with previous glucocorticoid toxicity, or pre-existing conditions likely to be exacerbated by glucocorticoids, who have not relapsed yet:</i> these are the patients who may be most in need of a new treatment option as TCZ is unavailable to them and they are by definition at very high risk of poor outcomes with current treatment. <i>Refractory/relapsing GCA patients, for whom TCZ is unsuitable, or not commissioned (eg because they have had one course of TCZ already):</i> these have relapsed but cannot have TCZ, so must instead prolong their glucocorticoid therapy, accumulating toxicity risk. Due to the safety profile of JAK inhibitors, clinicians may avoid prescribing UPA in certain patient sub-groups, in the same way that any prescribing decision in medicine involves a weighing up of risks against anticipated benefits for the individual patient given their own personal risk profile, values and preferences.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	See above for fuller explanation of: A daily oral therapy (tablets) may be more acceptable to some patients than weekly self-administered subcutaneous injections (TCZ).

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

18 of

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)	2. Patients taking long-term glucocorticoids need extensive “monitoring and mitigating” of risks and adverse effects. Current “monitoring and mitigating” practices are variably implemented, due to being complex and burdensome for patients and professionals. By allowing glucocorticoids to be stopped sooner, the technology will make it simpler and easier to manage patients. 3. Compared to TCZ, it will be easier for clinicians to evaluate patients for possible GCA relapse, using blood testing rather than expensive and difficult-to-access vascular imaging tests.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As discussed above, I envisage that decisions to start treatment with UPA will, at least in the first years, be made by rheumatologists after discussion with expert colleagues, in the same way as currently implemented for TCZ, and using the same regional MDT structures, based at specialist centres, as are currently in existence. Rigid implementation of “stopping rules” might produce unintended consequences, such as “tapering” to lower, unlicensed doses in an attempt to extend treatment, rather than “coming to a hard stop” no matter whether the patient is currently relapsing or not (Quick et al., 2025). Instead, decisions to extend treatment beyond a predetermined period (eg: after one year of glucocorticoid-free sustained remission) will be made by discussion with the regional MDTs at specialist centres. The regional MDTs will also be able to audit practice and build regional expertise rapidly by pooling experience across the region. This discussion step with regional colleagues would not need any extra tests. Quick V, Sah S, Dubey S, Mercer L, Nair JR, Coath FL, Kurshid M, Abusalameh M, Ahmed S, Alkoky H, Bukhari M, Carter S, Davidson B, Doddamani P, Ducker G, Griffiths B, Gullick N, Heaney J, Holloway A, Htut EEP, Hughes M, Irvine H, Kinder

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

19 of

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17. 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? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	As mentioned above, an <i>oral treatment</i> will be more acceptable to many patients than self-administered subcutaneous injection. I would expect that <i>reduced cumulative glucocorticoid dose</i> will produce health-related benefits, but these might not be fully captured in the QALY calculation. Late toxicity of glucocorticoids such as fragility fracture (the risk of which persists even after stopping glucocorticoids) will not be fully captured in the data from the clinical trial itself. The modelling required to estimate the ICER would need an appropriate model structure to model all the different adverse effects (with different timecourses) and would need to be parameterised from routinely-collected health data, which is limited by confounding by indication, data not missing at random, etc. It would be very difficult to model every single one of the fifty or so adverse effects listed in NICE CKS, and yet multiple small adverse effects can combine to produce an overall severe impact on physical and mental health. In terms of measurement instruments, I have some doubts as to whether <i>EQ-5D-5L as a measurement instrument</i> is sufficiently sensitive to discriminate true differences in glucocorticoid-related impacts on health-related quality of life in a clinical trial context. My doubts come from prior research projects I have worked on, some of which are cited below, in which we identified a gap in the measurement of the true health-related quality of life impact in relation to glucocorticoid therapy. I reviewed patient-reported outcome data in detail from studies of polymyalgia rheumatica, a related disease which is also treated with long-term glucocorticoid therapy. In phase 2 trials, the SF-36 physical component summary score

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

20 of

	appears to be sensitive enough to pick up improvements related to reduced cumulative glucocorticoid dose (Bonelli et al, 2022) but EQ-5D-5L was not (Bolhuis et al., 2023). With the larger numbers afforded by a phase 3 trial, the EQ-5D-5L signal does begin to emerge, but does not seem as clear-cut as changes in FACIT-F or SF-36-PCS (Strand et al., 2025). Black RJ, Robson JC, Goodman SM, Hoon E, Lai LYH, Simon LS, Harrison E, Neill L, Richards P, Nelsen LM, Nebesky JM, Mackie SL, Hill CL. A Patient-reported Outcome Measure for Effect of Glucocorticoid Therapy in Adults with Inflammatory Diseases Is Needed: Report from the OMERACT 2016 Special Interest Group. <i>J Rheumatol</i>. 2017 Nov;44(11):1754-1758. doi: 10.3899/jrheum.161083. Epub 2017 Apr 1. PMID: 28365575. Cheah JTL, Robson JC, Black RJ, Goodman SM, Lester S, Mackie SL, Hill CL. The patient's perspective of the adverse effects of glucocorticoid use: A systematic review of quantitative and qualitative studies. From an OMERACT working group. <i>Semin Arthritis Rheum</i>. 2020 Oct;50(5):996-1005. doi: 10.1016/j.semarthrit.2020.06.019. Epub 2020 Jul 13. PMID: 32911291. Bridgewater S, Shepherd MA, Dawson J, Richards P, Silverthorne C, Ndosi M, Almeida C, Black RJ, Cheah JTL, Dures E, Ghosh N, Hoon EA, Lyne S, Navarro-Millan I, Pearce-Fisher D, Ruediger C, Tieu J, Yip K, Mackie SL, Goodman S, Hill C, Robson JC. Measuring the impact of steroid therapy on health-related quality of life in patients with rheumatic diseases: international development of a glucocorticoid treatment-specific patient-reported outcome measure.

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

21 of

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18. Do you consider the technology to be innovative in its potential to make a significant and substantial	I think this technology fills a major unmet need for my GCA patients, who currently have extremely restricted options for treatment of their disease.

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

22 of

impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	It will not be suitable for every patient, but it is important to have options available. The difference is enough to make a "step-change". It addresses the unmet need for effective treatment while being able to taper glucocorticoid dose safely.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	From experience prescribing this treatment for other indications, it is well-tolerated compared to glucocorticoids. There are however some known safety concerns with the class of JAK inhibitors and these are discussed above. The magnitude of the risk with this treatment is likely to be quite small in comparison to the risks and burdens patients already face with glucocorticoid therapy, and the clinical view of the balance of risk is likely to evolve with practical experience of using this treatment in practice.
20. Do the clinical trials on the technology reflect current UK clinical practice? - 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? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	- SELECT-GCA is a global trial and broadly reflects UK clinical practice in terms of the patient population we would consider for this drug. - The most important outcome in my opinion is sustained remission of GCA and this was the primary outcome of the trial. If the trial were being conducted today, I would also have liked to see glucocorticoid-related adverse effects measured using a specific tool such as the Glucocorticoid Toxicity Index (clinical impacts of glucocorticoids) and the Steroid PRO (impact of glucocorticoid on patients' lives) but the latter was not available at the time the trial was designed. - Surrogate outcomes were not used. - A clinical trial of a different member of the JAK inhibitor class (tofacitinib), in a different disease (rheumatoid arthritis), identified safety concerns (cardiovascular disease, malignancy) with this drug class that has been evaluated by the regulators and resulted in a "black box warning". The applicability of these data to this drug in this disease is not clear, but conservatively most clinicians will likely assume the "black box warning"

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

23 of

	applies here. This has already been embedded into prescribing guidance for UPA in its other licensed indications. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, Germino R, Menon S, Sun Y, Wang C, Shapiro AB, Kanik KS, Connell CA; ORAL Surveillance Investigators. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. N Engl J Med. 2022 Jan 27;386(4):316-326. doi: 10.1056/NEJMoa2109927. PMID: 35081280.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. How do data on real-world experience compare with the trial data?	I am not aware of any real-world (post-marketing) experience with UPA in GCA as yet.
23. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with giant cell arteritis are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	The current safety concerns about JAK inhibitors pertain to the over-65s. Upadacitinib is licensed for the over-65s but with a “black box warning” to reflect the safety concerns. As post-marketing data continues to accumulate on all drugs in the JAK inhibitor class, the prescribing guidance may update in coming years. Therefore, if NICE chooses to recommend commissioning of this technology UPA for patients with GCA, I do not think that NICE should put an upper age limit to its recommendation, as clinicians must always prescribe in line with latest evidence in any case; I think that the recommendation should be applicable to patients of any age. There are some sub-groups of patients with GCA that are more likely to relapse (those that have had large vessel involvement demonstrated on vascular imaging), but if this were incorporated into the recommendation, there would be some equality concerns with the implementation of this. In the NHS, access to vascular imaging can be restricted for some patients, mainly due to variations in local service provision as well as protected characteristics eg disability that may

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

24 of

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	make it difficult for some patients to travel to specialist centres for tests or undergo certain scans.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. GCA is a chronic disease, but current treatment for GCA, high-dose, long-term glucocorticoids, are so toxic that they must be withdrawn (“tapered”) despite the high risk that this will induce relapse.
2. The unmet need is starkest for patients with GCA who have had previous glucocorticoid toxicity, or who have pre-existing conditions likely to be worsened by glucocorticoid toxicity; and for those who cannot access tocilizumab either due to contra-indication or because they have had one year already.
3. Tocilizumab, the current standard of care for relapsing/refractory GCA, stops us being able to monitor GCA disease activity using blood tests; if patients develop symptoms as they continue to taper their glucocorticoids, costly and burdensome imaging tests can be needed to confirm or refute GCA relapse.
4. From the published clinical trial data, this new technology improves physical health-related quality of life, and fatigue, which are two major symptoms that impacts on my patients’ quality of life.

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Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

27

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Single Technology Appraisal

Upadacitinib for treating giant cell arteritis [ID6299]

Clinical expert statement

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In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as '**confidential [CON]**' in turquoise, and all information submitted as '**depersonalised data [DPD]**' in pink. If confidential information is submitted, please also

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Friday 5 September 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating giant cell arteritis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Fiona Coath
2. Name of organisation	- British Society for Rheumatology - Norfolk and Norwich University Hospital
3. Job title or position	- Co-convenor of the British Society for Rheumatology vasculitis and polymyalgia rheumatica specialist interest group (SIG), Chair of the Group since May 2025. - Rheumatology Consultant in the vasculitis unit at Norfolk and Norwich University Hospital.
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 giant cell arteritis? ☒ A specialist in the clinical evidence base for giant cell arteritis 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 did not submit one, I do not 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

Clinical expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

Single Technology Appraisal

Upadacitinib for treating giant cell arteritis [ID6299]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

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Part 1: Living with this condition or caring for a patient with giant cell arteritis

Table 1 About you, giant cell arteritis, current treatments and equality

1. Your name	Fiona Johnson
2. Are you (please tick all that apply)	☒ A patient with giant cell arteritis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with giant cell arteritis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	PMRGCAuk
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I run the telephone helpline on behalf of PMRGCAuk so regularly receive calls from people experiencing problems with current treatments for GCA – I also co-run a support

Patient expert statement

	group in my region meaning I have their opinions and views of current treatments available. ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with giant cell arteritis? If you are a carer (for someone with giant cell arteritis) please share your experience of caring for them	It is a frustrating and debilitating disease, and my personal experience is that this is compounded by a lack of knowledge or understanding of the condition by the public or many frontline health professionals. This means that it requires you to become an expert in your own condition and then it becomes additionally frustrating that the very professionals who know little about the condition don't listen to the patient sufficiently as they assume that as the patient is not medically qualified, they are therefore not equipped to understand how the condition should be treated. There is particularly little advice given to patients about how to manage the condition outside of taking the steroids. This means that people often develop issues with mobility (steroids cause muscle weakness) and mood/sleep with little to no support. It is also very stressful to live with a condition where one knows that blindness is a possible side-effect which often results in people having high levels of anxiety
7a. What do you think of the current treatments and care available for giant cell arteritis on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	7a. It is frustrating that the major treatment is a drug that has many negative side effects and the main response to this is to offer further medication. At the age of 60 I was not taking any medication – 8 years later I am taking steroids for GCA but also blood pressure medication, alendronic acid, methotrexate, omeprazole and blood thinners for a DVT which was likely caused by taking the steroids. I am also at risk of steroid induced Type 2 diabetes for which further medication will be provided. It was very frustrating to be told by a GP Pharmacist that my diabetes was probably steroid induced and that therefore the only solution was to stop taking steroids and/or take metformin with apparent little understanding of the effort that had I already taken to try and reduce steroids. There was also an expectation that the

Patient expert statement

	rheumatologist should be sorting this when I knew that she was doing everything she could but with a limited range of resources at her disposal. 7b All of the people I know with GCA and PMR are frustrated that the only drug that is routinely offered is one that causes so many side effects and are concerned, as I am, that there seems to have been so little research into alternative treatments.
8. If there are disadvantages for patients of current NHS treatments for giant cell arteritis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The main treatment for GCA is steroids – prednisolone or equivalent. The potential side effects are steroid induced type 2 diabetes, weight gain, internal damage to the stomach lining, steroid induced hyper-tension, osteopenia and osteoporosis, DVTs. All of these are risks for long term use of steroids, so patients are routinely prescribed omeprazole and alendronic acid as well as calcium, folic acid and vitamin D supplements. There are then side effects experienced from long term use of the drugs being taken to protect the patient from the steroids which mean that the patient ends up taking more drugs to manage the condition. For example, after long term use of omeprazole I tried to stop because my steroid dose was so low it was no longer warranted but then found I was experiencing extreme acid reflux and found that this was a side effect of ceasing to take the omeprazole because I had been taking it for a long time. Thus, a drug taken initially to protect the stomach lining ends up causing gastric problems.
9a. If there are advantages of upadacitinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does upadacitinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	9a I have no personal experience of Upadacitinib (UPA) but know people who have been able to take Tocilizumab (TCZ) and have found it has enabled them to reduce their steroid dosage more quickly. If UPA has the same effect, then that would be helpful particularly since UPA is a tablet and does not require injections. I am taking methotrexate to help my steroid reduction and whilst this was helpful when I was on higher doses of steroids it seems less effective on lower doses, and my personal experience is of repeated flare-ups requiring a return to higher doses of both methotrexate and steroids. I am wary of TCZ because of the limit of one year's treatment; a concern that I know is shared by other patients, and some clinicians, as there is no guarantee that the condition will disappear within that time scale. I am also not keen on a treatment that requires regular injections. 9b A major advantage is that it provides an alternative to TCZ that is more accessible as it can be taken in tablet form.

Patient expert statement

	9c I am not fully aware of side effects from UPA but as far as I know it does not cause diabetes, osteoporosis or DVTs so as such it would be an improvement on steroid use.
10. If there are disadvantages of upadacitinib over current treatments on the NHS please describe these. For example, are there any risks with upadacitinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have no personal knowledge of side effects from UPA. I have read that there is a risk of major adverse cardiac events but that there has been differing reports from different clinical trials as to the risk that is posed – I would expect this to be something that needs careful consideration.
11. Are there any groups of patients who might benefit more from upadacitinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	UPA will provide all patients with GCA a choice of steroid sparing treatments and would be most useful to those, like me, who have recurring flare-ups that do not respond well to current more conservative treatments.
12. Are there any potential equality issues that should be taken into account when considering giant cell arteritis and upadacitinib? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equality issues can be found in the NICE equality scheme	GCA affects older women disproportionately and this is a group of people who have traditionally been neglected by the medical profession who have historically been over-represented by younger men.

Patient expert statement

[Find more general information about the Equality Act and equalities issues here.](#)

13. Are there any other issues that you would like the committee to consider?

Patient expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Current treatment for GCA is mainly concentrated on steroids that have significant negative side effects for the patient, particularly for those whose GCA is recurrent and does not respond quickly to the treatment.
- Current treatment options apart from steroids are limited to a very few steroid sparing drugs which also have significant side effects meaning they do not suit everyone.
- The other major biologic drug TCZ has to be administered as an injection which is not easy for the patient and it is also limited to one year's treatment making it unpopular with patients whose condition is long-standing and recurring.
- UPA appears to offer patients a choice of treatments which is useful for those who cannot use current medications.
- UPA is available in a tablet form making it more accessible to those people who are needle phobic or may struggle to self-medicate using needles.

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Single Technology Appraisal

Upadacitinib for treating giant cell arteritis [ID6299]

Patient expert statement

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Patient expert statement

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Part 1: Living with this condition or caring for a patient with giant cell arteritis

Table 1 About you, giant cell arteritis, current treatments and equality

1. Your name	Mrs Maxine Wright
2. Are you (please tick all that apply)	☒ A patient with giant cell arteritis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with giant cell arteritis? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Vasculitis UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference

Patient expert statement

	☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with giant cell arteritis? If you are a carer (for someone with giant cell arteritis) please share your experience of caring for them	6 I was first diagnosed with Giant Cell Arteritis/ Large Vessel Vasculitis aged 55 years, in August 2015. My diagnosis followed 6 months of being ‘unwell’ and misdiagnosis along the way, eg Migraine, Polymyalgia Rheumatica. My symptoms were many and varied, but an intermittent loss of vision in my right eye caused me to seek a medical opinion. My GP ordered, bloods which showed a raised CRP and ESR – she immediately commenced 60mgs of Prednisolone and prophylactic soluble Aspirin 75mgs and thought perhaps I had Polymyalgia Rheumatica. Other symptoms prior to diagnosis included, a stiff neck, aches/ pains in muscles/joints, shooting pains in my head coming up from the occipital region which would settle as a frontal headache. Fainting sometimes more than once a day which on three occasions resulted in A and E trips as I couldn’t bring my blood pressure back up. I suffered with cramp in my arms, hands and legs and, had an inability to lift my arms up, as they felt so heavy. I would use my left arm to lift my dominant right arm to do tasks eg Hang out washing. Night sweats were disturbing, with which I had a significant weight loss, but had been dieting! I experienced minimal temporal pain and occasional jaw claudication. I had a rash on my chest which was thought to be a side effects of drugs. However, the rash followed a pattern where the blood vessels were inflamed and has now completely cleared. The collapses increased in frequency, and I became frightened by them as I feared I would never ‘come to’. They were unpredictable, both when they would occur and how long they lasted. I had absent radial pulses and a bruit. I would feel tachycardic with ectopic beats and my hands would become cyanosed which generally preceded a faint as my blood pressure dropped. My BP recordings differed in each arm. On more than one occasion I saw blood vessels balloon, swell and bulge. I did not realise, at that stage, those blood vessels were close to occluding. This bulging occurred in my scalp and my left forearm. Finally, an MRI showed inflammation of my axillary and subclavian blood vessels. My temporal artery showed resolving inflammation, but by the time this investigation took place I had been taking Steroids

Patient expert statement

	for 6 weeks. Subsequent scans years later show damage to my Ophthalmic ICA. I am grateful, so far, that my aorta was spared. One of the hardest things to live with was the fatigue. I was beyond tired. I would wake up as tired and not rested. I would be stiff and ache all over on rising to shower, after which I needed to go back to bed for a couple of hours to recover. The symptoms lasted for months, even when on treatment. It was a life changing, debilitating experience and at times overwhelming both for myself and my family. I couldn't do simple tasks other than wash and dress myself. I couldn't drive anywhere for months due to cramp in my arms/ legs and fainting. We needed to employ help in the home as I was unable to manage household chores such as cooking and simply keeping the house clean. I became very anxious fearing the next collapse and I felt I would not make my 56th birthday. I was normally a very capable, career woman, working full time with a positive attitude to life. At this acute stage I felt I lost my health, my life and my future. I was truly terrified but fortunately surrounded by a supportive husband and family. I ceased steroids in 2017, after two years, due to needing thyroid surgery. I had a benign growth on my left lobe which required a hemithyroidectomy. The tumour was beginning to affect my breathing and was the size of a fist. I recommenced Methotrexate post operatively and remain on it to date. I returned to work after 4 months, but remained unwell for around two years. I talk about my life in terms of before and after Vasculitis, such is the impact of the illness. Although, now in drug induced remission, and living an active life I describe myself as living as if I have an imp or devil peering over my shoulder. In other words, it feels as if Vasculitis is always there, waiting in the wings armed with an acute attack, waiting to strike again anytime.
7a. What do you think of the current treatments and care available for giant cell arteritis on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	7a In my experience the current treatment relies heavily on steroid therapy which brings complications which the patient has to be mindful of or manage. Potential weight gain, risk of secondary Diabetes, adrenal insufficiency, immunosuppression and osteoporosis to name the most common. I went from taking no medication at all to taking 10+ different medications, most of which were to counteract Steroid and Methotrexate use. I continue to take 9 of them today.

Patient expert statement

	Steroid reduction can be a challenge due to flares and not always well managed with good clinical support. My diagnosis was pre covid and it still took over a month as an inpatient for an experienced Rheumatologist to diagnose me. I requested for a second opinion as a Locum Rheumatologist stopped my steroids and attempted to discharge me. I do appreciate the difficulties around diagnosis, but I knew how ill I felt. At that stage I was classed as too young for GCA, yet too old for Takayasu. I am now seen at Imperial College London where the symptoms I describe are believed and more importantly the disease understood. I fear for those patients who do not have access to the correct expertise. There is a risk of permanent damage to eyesight, blood vessels and associated organs or loss of life. I totally understand it is difficult to diagnose, but access to the right medication, knowledgeable professionals is essential and cost effective. 7b Whilst other GCA and Vasculitis patients may present differently to me much of the experience is similar, with high dose steroids, given with an additional a chemotherapy drug such as Methotrexate or Azathioprine. Getting diagnosed can be difficult, along with the lack of support following diagnosis from either nursing or medical staff can cause additional distress. Good GP support is essential can be hard to access but again is variable.
8. If there are disadvantages for patients of current NHS treatments for giant cell arteritis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	8 Again, steroids and the side effects of them feature here. I felt energised on Steroids for a few days but quickly became fatigued again. In addition to the side effects listed earlier, some patients I know of have experienced depression and psychological symptoms, including instances of suicide. I became increasingly anxious on treatment, but this was also due to the unpredictable nature of the disease symptoms. I took my medication orally and in the main tolerated these well except for some nausea which gradually receded. I personally would not have had an issue injecting medication if it saved my life.
9a. If there are advantages of upadacitinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your	9 a Not known. I have not taken this medication.

Patient expert statement

ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does upadacitinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	However, a potential reduction to 26 weeks in taking steroid therapy would be a clear advantage improving people's quality of life, 9 b No comment 9 C
10. If there are disadvantages of upadacitinib over current treatments on the NHS please describe these. For example, are there any risks with upadacitinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	10. I note there are some risks for people taking this medication if they have a pre-existing cardiac problem or blood clots. Given the inflammatory nature of GCA and the subsequent damage to blood vessels and organs from an out-of-control autoimmune system, what are the consequences of NOT taking this medication and how is this discussed with patients? From my perspective, I would consider myself, more at risk to cardiac/neurological events, because of narrowed and damaged blood vessels. I may be coming from a position of living with and understanding the disease. However, as a patient I would value an honest conversation about the risks/benefits of taking the medication and appropriate monitoring whilst taking it.
11. Are there any groups of patients who might benefit more from upadacitinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	11. I have a sense that patients who may benefit more from Upadacitinib could be those who predispose to Diabetes or have a family history of it. This medication could reduce time spent on steroid therapy down to 26 weeks as opposed to being 2 years or more therefore reducing the risk of tipping into Diabetes Mellitus. In my view patients with a cognitive impairment or other health conditions may benefit from taking this medication too but may require additional support from a carer or family member to ensure correct administration and monitoring. The risks with other co morbidities would of course need to be a clinical decision.

Patient expert statement

12. Are there any potential equality issues that should be taken into account when considering giant cell arteritis and upadacitinib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	None I am aware of.
13. Are there any other issues that you would like the committee to consider?	Please ensure there are support / monitoring systems in place for patients beginning this medication and on going.

Patient expert statement

Upadacitinib for treating giant cell arteritis [ID6299]

8 of 9

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is a need for an effective alternative to long term steroid therapy
- A need for quicker diagnosis and equal access to appropriate treatment.
- For a better understanding of GCA and its associated risks in primary and secondary care. There appears to be a tendency to dismiss GCA and PMR as an older person's condition, almost expected as part of getting older.
- A need for quicker recovery time, and opportunity to return to an active life as quick as possible.
- A requirement for health and Social Care professionals to understand the impact of this disease on people and to consider what on going support may be required.

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Upadacitinib for treating giant cell arteritis [ID6299]

External Assessment Group (EAG) Report

Title: Upadacitinib for treating giant cell arteritis [ID6299]

Produced by	<i>Centre for Evidence and Implementation Science (formerly Warwick Evidence), University of Birmingham</i>
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Date completed	<i>18/08/2025 (post factual accuracy check)</i>

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Declared competing interests of the authors

None.

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Contributions of authors

Ewen Cummins critiqued the company model, corrected identified errors and undertook EAG economic modelling. Martin Connock carried out EAG's examination of company's extrapolation of data and conducted analyses using reconstructed IPD data. Adel Elfeky and Iman Ghosh critiqued the clinical effectiveness evidence. Naila Dracup critiqued the company's searches and conducted additional EAG searches. Yen-Fu Chen coordinated the EAG team, critiqued the decision problems and contributed to adjusted indirect comparisons. All authors contributed to the writing and editing of the report.

Please note that: Sections highlighted in [REDACTED] are [REDACTED]. Sections highlighted in [REDACTED]. Figures that are CIC have been bordered with blue.

Abbreviations

ABA	Abatacept
ACE	Angiotensin-Converting Enzyme
AE	Adverse effect / adverse event
AIC	Akaike Information Criterion
AUC	Area under the curve
BSR	British Society for Rheumatology
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
cPAS	confidential Patient Access Scheme
CPRD	Clinical Practice Research Datalink
CRD	Centre for reviews and dissemination
CS	Company submission
CS-T	Corticosteroid tapering
CTA	Computed tomography angiography
CTCAE	Common Terminology Criteria for Adverse Events
EAG	External Assessment Group
EMIT/eMIT	Drugs and pharmaceuticals electronic market information tool
EQ-5D	EuroQoL five dimension
EULAR	The European Alliance of Associations for Rheumatology
FACIT	Functional Assessment of Chronic Illness Therapy
FAC	Factual accuracy check
FAD	Final appraisal document
FF	First flare
GC	Glucocorticoids
GCA	Giant cell arteritis
GC-T	Glucocorticoid tapering
GRAE	Grading of Adverse Events
GIRFT	Getting It Right First Time
HCRU	Healthcare resource utilization
HRQoL	Health-related quality of life
HTA	Health technology appraisal

ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
IL	Interleukin
IOP	Intraocular Pressure
IPD	Individual patient data
IRP	International Recognition Procedure
ITC	Indirect treatment comparison
ITT	Intention to treat
JAK	Janus kinase
K-M/KM	Kaplan-Meier
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MHRA	Medicines & Healthcare products Regulatory Agency
MRA	Magnetic resonance angiography
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSTEMI	Non-ST-Segment Elevation Myocardial Infarction
OP	Outpatient
PBO/PLAC	Placebo
PET	Positron emission tomography
PICOS	Population, Interventions, Comparators, Outcomes, and Study design
PMR	Polymyalgia rheumatica
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS	Personal social services
QALY	Quality adjusted life year
RCT	Randomised control trial
RoB	Risk of bias
ROBINS	Risk Of Bias In Non-randomised Studies
RR	Risk ratio

RWE	Real world evidence
SAE	Serious adverse events
SLR	Systematic literature review
SmPC	Summary of product characteristics
T2DM	Type 2 diabetes mellitus
TCZ	Tocilizumab
TCZ QW	Tocilizumab weekly
TEAE	Treatment emergent adverse events
TTFF	Time to first flare
TTSF	Time to subsequent flare
UK	United Kingdom
UPAD	Upadacitinib
US	United States
VTE	Venous thromboembolism

Contents

Executive Summary	13
1.1 Overview of the EAG's key issues	15
1.2 Overview of key model outcomes	18
1.3 The decision problem: summary of the EAG's key issues	18
1.4 The clinical effectiveness evidence: summary of the EAG's key issues	20
1.5 The cost-effectiveness evidence: summary of the EAG's key issues	21
1.6 Other key issues: summary of the EAG's view	27
1.7 Summary of EAG's preferred assumptions and resulting ICER.....	27
External Assessment Group Report.....	30
1 INTRODUCTION AND BACKGROUND	30
1.1 Introduction	30
1.2 Background.....	30
1.2.1 Condition, symptoms and economic burden	30
1.2.2 Clinical pathway and unmet needs	32
1.2.3 Positioning of upadacitinib	33
1.3 Critique of company's definition of decision problem	34
2 CLINICAL EFFECTIVENESS.....	43
2.1 Critique of the methods of review(s)	43
2.1.1 Searches.....	44
2.1.2 Inclusion criteria	45
2.1.3 Selection of the included studies	45
2.1.4 Critique of data extraction	46
2.1.5 Quality assessment	46
2.1.6 Evidence synthesis	47
2.1.7 Additional work on SLR undertaken by the EAG	48
2.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these).....	48
2.2.1 SELECT-GCA.....	49
2.2.2 Risk of bias SELECT-GCA	50
2.2.3 Efficacy results SELECT-GCA.....	52
2.2.4 Safety SELECT-GCA.....	53
2.2.5 Subgroup analysis	54
2.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison.....	55
2.4 Critique of the indirect comparison and/or multiple treatment comparison.	55
2.5 Additional work on clinical effectiveness undertaken by the EAG	56
2.5.1 EAG's exploration of the company's time to event (flare) analyses	56
2.5.2 Adjusted indirect comparison between upadacitinib and tocilizumab .	88
2.6 Conclusions of the clinical effectiveness section.....	104
3 COST EFFECTIVENESS.....	106
3.1 EAG comment on company's review of cost-effectiveness evidence	106
3.1.1 Search strategy.....	106
3.1.2 Study selection criteria, quality assessment and synthesis.....	107
3.2 Summary and critique of the company's submitted economic evaluation by the EAG	107

3.2.1	NICE reference case checklist.....	107
3.2.2	Model structure	109
3.2.3	Baseline cumulative steroid dose	113
3.2.4	Interventions and comparators	114
3.2.5	Perspective, time horizon and discounting.....	115
3.2.6	Treatment effectiveness and extrapolation	115
3.2.7	Discontinuations	139
3.2.8	Health related quality of life.....	140
3.2.9	Resources and costs	140
4	COST EFFECTIVENESS RESULTS	144
4.1	Cost basis	144
4.2	Company base case cost effectiveness results	144
4.3	Company subgroup analysis.....	146
4.4	Company sensitivity and scenario analysis.....	146
4.5	Model validation and face validity check	146
4.5.1	EAG cross check model rebuild.....	146
4.5.2	EAG corrected company base case: Scenario analyses	151
4.5.3	Model validation	152
5	EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES	153
5.1	EAG critique of economic modelling compared to position sought	153
5.1.1	What is the relevance of the company base case economic modelling? 153	
5.1.2	SELECT-GCA Period 2 data.....	153
5.1.3	Model structure and treatment sequencing.....	154
5.2	EAG critique of elements of the company model	155
5.2.1	Age at baseline	155
5.2.2	New onset modelling choice of TTFF curves	156
5.2.3	New onset modelling waning of treatment effect	160
5.2.4	Incidence of subsequent flares	162
5.2.5	Conditions related to GCA flares	162
5.2.6	Conditions exacerbated by steroid use and cumulative steroid use .	164
5.2.7	Conditions exacerbated by steroid use: SELECT-GCA placebo arm compared to company market survey	166
5.2.8	Adverse events associated with upadacitinib use.....	172
5.3	EAG critique of the handling of quality of life within the model.....	172
5.3.1	Main quality of life values	172
5.3.2	Duration of transient conditions	173
5.4	EAG critique of the handling of costs within the model	173
5.4.1	Monitoring costs.....	173
5.4.2	Costs of conditions related to GCA flare, to steroid use and to upadacitinib use	174
5.5	Minor issues.....	177
5.5.1	Minor Issue: Baseline steroid distributions.....	177
5.5.2	Minor issue: Bilateral visual loss costs.....	177
5.5.3	Permanence of minor stroke.....	178
5.6	Exploratory and sensitivity analyses undertaken by the EAG	178
5.6.1	EAG model revisions	178
5.6.2	EAG scenario analyses.....	186
5.7	Conclusions of the cost effectiveness section.....	188

6	SEVERITY MODIFIERS	189
7	REFERENCES.....	189
8	APPENDICES	200

Table of tables

Table 1: Summary of key issues	15
Table 2: Company base case cost effectiveness estimates: Deterministic	18
Table 3: EAG corrections to company base case	28
Table 4: EAG changes: pairwise cost effectiveness estimates vs placebo	29
Table 5: Summary of decision problem	35
Table 6: Summary of the EAG's critique of the company's SLR	43
Table 7: Comparison of company and EAG risk of bias assessment of SELECT-GCA	50
Table 8: Akaike Information Criteria scores for parametric models of corrected K-M	64
Table 9: AIC scores for parametric models of new onset subgroup	68
Table 10: AIC scores for parametric models of relapsing subgroup	73
Table 11: Estimates of restricted mean survival, intervention versus PBO	85
Table 12 AUC estimates for lognormal models of ITT intervention and placebo treatments	87
Table 13: AUC estimates for Gompertz models of ITT intervention and placebo treatments.	87
Table 14: Demographic and disease characteristics for study participants at baseline: SELECT-GCA vs GiACTA	89
Table 15: Adjusted indirect comparison for upadacitinib vs tocilizumab.....	90
Table 16: Comparative data for cumulative steroid dose from SELECT-GCA and GiACTA trial.....	92
Table 17: Restricted mean survival estimates to 51 weeks according to intervention and trial	94
Table 18: AUC estimates for lognormal models of ITT intervention and placebo.....	96
Table 19: AUC estimates for Gompertz models of ITT intervention and placebo.....	96
Table 20: Estimates of restricted mean survival, intervention versus PBO	102
Table 21: AUC estimates for lognormal models of ITT intervention and placebo treatments	104
Table 22: AUC estimates for Gompertz models of ITT intervention and placebo treatments.	104
Table 23: NICE reference case checklist	108
Table 24: Baseline patient characteristics	113
Table 25: ITT: Time to first flare curves' information criteria.....	117
Table 26: New Onset subgroup: Time to first flare curves' information criteria	121
Table 27: Relapsed subgroup: Time to first flare curves' information criteria	125
Table 28: GCA flare related conditions' probabilities, cost and quality of life	128

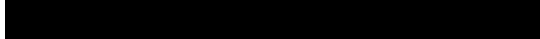
Table 29: Steroid related conditions that last one year, annual probability, cost and QALY.....	130
Table 30: Steroid related conditions that are permanent, annual probability, annual cost and annual quality of life effect	131
Table 31: Calculation of daily steroid dose to be added to cumulative total	134
Table 32: Upadacitinib JAK adverse events' probability, cost and QALY.....	139
Table 33: Quality of Life: No flare and with flare.....	140
Table 34: Direct drug costs	141
Table 35: Prednisolone costs per mg	141
Table 36: Balance and costs of different types of visit when not in flare	142
Table 37: Balance and costs of different types of visit when not in flare	143
Table 38: Balance and costs of different types of visit when in flare	143
Table 39: Company base case: Costs.....	144
Table 40: Company base case: QALYs	145
Table 41: Company base case: Summary	145
Table 42: EAG corrected company base case: Disaggregate cost offsets.....	147
Table 43: EAG corrected company base case: Disaggregate cost offsets.....	148
Table 44: EAG corrected company base case: Disaggregate QALYs	149
Table 45: EAG corrected company base case: Costs.....	150
Table 46: EAG corrected company base case: QALYs.....	150
Table 47: EAG corrected company base case: Summary.....	150
Table 48: Scenarios around EAG corrected company base case	152
Table 49: New onset: Proportion of baseline patients that are flare free: upadacitinib	157
Table 50: New onset: Proportion of baseline patients that are flare free: placebo ..	158
Table 51: New onset: Proportion of surviving patients that are flare free: upadacitinib	158
Table 52: New onset: Proportion of surviving patients that are flare free: placebo.	159
Table 53: New onset: Proportion successfully tapering who are flare free at 10 years	159
Table 54: Company incidences of new diagnoses of osteoporosis	165
Table 55: Subset of conditions exacerbated by steroid use: SELECT-GCA vs company market survey	167
Table 56: EAG changes: pairwise cost effectiveness estimates vs placebo	178
Table 57: EAG base case: Disaggregate cost offsets: ITT.....	179
Table 58: EAG base case: Disaggregate QALYs: ITT population	180
Table 59: EAG base case: Costs: ITT population	180
Table 60: EAG base case: QALYs: ITT population	181
Table 61: EAG base case: Summary: ITT population	181
Table 62: EAG base case: Costs: new onset subgroup	182
Table 63: EAG base case: QALYs: new onset subgroup.....	183
Table 64: EAG base case: Summary: new onset subgroup	183
Table 65: EAG base case: Costs: relapsed subgroup.....	184
Table 66: EAG base case: QALYs: relapsed subgroup.....	185
Table 67: EAG base case: Summary: relapsed subgroup.....	185
Table 68: EAG scenario analyses	187
Table 69: ROBINS assessment	209
Table 70: Risk of bias assessment of randomised controlled trials using revised Cochrane risk of bias tool (RoB2)	212

Table 71: Full set of conditions exacerbated by steroid use: SELECT-GCA vs company market survey	219

Table of figures

Figure 1: Company's Corrected K-M plots for ITT PBO and Upadacitinib TTFF	59
Figure 2: EAG KM plots based on data supplied in clarification.	60
Figure 3: Company's Corrected K-M plot for ITT PBO TTFF compared to that originally submitted K-M (red line).....	61
Figure 4: Changing trajectory in the PBO K-M plot (blue line).....	62
Figure 5: Smoothed hazard plot for corrected ITT PBO TTFF	63
Figure 6: Parametric models for ITT PBO population (Weibull, loglogistic, Gompertz, exponential, bathtub, Chen and Rayleigh models over observed data range)	65
Figure 7: Lognormal and generalised gamma models for ITT PBO.	65
Figure 8: Parametric models for ITT upadacitinib population Weibull, loglogistic, Gompertz, exponential, bathtub, Chen, lognormal and Rayleigh models over observed data range (the lognormal model is indicated by the thick blue line)	66
Figure 9: Parametric models extrapolated to 30 years (PBO).....	67
Figure 10: Parametric models extrapolated to 30 years (Upadacitinib).....	67
.....	69
.....	70
.....	Error! Bookmark not defined.
.....	72
.....	73
.....	Error! Bookmark not defined.
.....	76
.....	Error! Bookmark not defined.
.....	Error! Bookmark not defined.
.....	78
.....	Error! Bookmark not defined.
.....	Error! Bookmark not defined.
Figure 23: Reconstructed PBO K-M for the relapsing subgroup of GiACTA followed for 3 years	80
Figure 24: Reconstructed PBO K-M for the new onset subgroup of GiACTA followed for 3 years	81
Figure 25: GiACTA K-M plots: comparison of tocilizumab versus PBO according to subgroup.	82
.....	Error! Bookmark not defined.
.....	Error! Bookmark not defined.

Figure 28: SELECT-GCA (upadacitinib vs PBO) and GiACTA (tocilizumab vs PBO) ITT populations: Kaplan-Meier graphs with Lognormal (upper panel) and Gompertz (lower panel) models extrapolated to 3 years.....	86
.....	91
Figure 30: Experiencing at least one flare at week 52 – results from SELECT-GCA and GiACTA trials ITT population.....	91
Figure 31: Reconstruct Kaplan-Meier plots based on GiACTA 52 weeks observed TTFF	93
Figure 32: Kaplan-Meier plots based on SELECT-GCA 52 weeks observed TTFF ..	93
Figure 33: Lognormal and Gompertz models fit to intervention and control arms of GiACTA	95
Figure 34: Lognormal and Gompertz models fit to intervention and control arms of SELECT-GCA	96
Figure 35: Reconstructed PBO K-M for the relapsing subgroup of GiACTA followed for 3 years	97
Figure 36: Reconstructed PBO K-M for the new onset subgroup of GiACTA followed for 3 years	98
Figure 37: GiACTA K-M plots: comparison of tocilizumab versus PBO according to subgroup	99
.....	101
Figure 39: Kaplan-Meier analyses of TTFF for Select GA and GiACTA ITT populations.....	101
Figure 40: Select GCA and GiACTA ITT populations: Lognormal and Gompertz models extrapolated to 3 years	103
Figure 41: Company model structure: © AbbVie (2025).....	109
Figure 42: Company base case overall survival: ITT population	114
Figure 43: Company TTFF curves: Upadacitinib: ITT.....	116
Figure 44: Company TTFF curves: Placebo: ITT	116
Figure 45: ITT: Proportions surviving and proportions flare free	118
Figure 46: ITT: Proportions of those surviving who are flare free	118
Figure 47: ITT Annualised flare incidences	119
.....	120
.....	121
.....	122
.....	123
.....	124
.....	125
.....	125
.....	126
.....	126
.....	127
Figure 58: Company base case mean daily steroid dose.....	133
Figure 59: Company ITT base case cumulative steroid dose per surviving patient	136
Figure 60: Company ITT base case cumulative steroid dose per surviving patient: Error 05 corrected	137
Figure 61: Company ITT base case cumulative steroid dose per surviving patient: Errors 05 and 06 corrected.....	138
.....	138

Figure 63: EAG corrected company base case CEAC	151
	156
	160
Figure 66: EAG base case: CEAC: ITT population	182
Figure 67: EAG base case: CEAC: new onset population.....	184
Figure 68: EAG base case: CEAC: relapsed subgroup.....	186

Executive Summary

This report summarises the critique of the company submission (CS), including the company's response to clarification questions, by the External Assessment Group (EAG). Key issues identified by the EAG include:

Decision problem: the company did not include tocilizumab in its submission and therefore did not consider its use in the treatment pathway for adult patients with giant cell arteritis (GCA). This was despite that tocilizumab was recommended for people with refractory/relapsing GCA in NICE TA518 subject to a one-year stopping rule, and the intended use of upadacitinib proposed by the company covered this place in the treatment pathway. The EAG therefore considered that inadequate evidence was presented in the CS to inform treatment decisions.

Clinical effectiveness evidence: The main clinical effectiveness evidence presented by the company was restricted to the year 1 data from its pivotal trial, SELECT-GCA which compared upadacitinib plus a 26-week schedule of steroid tapering with a 52-week schedule of steroid tapering. While data from the trial clearly demonstrated the effectiveness of upadacitinib in maintaining remission and reducing flare compared with placebo, company did not provide any comparative evidence between upadacitinib and tocilizumab in the CS (as mentioned above), which hinders on the EAG assessment of clinical effectiveness involving people with relapsing/refractory GCA. Within the time constraint, EAG provides some preliminary adjusted indirect comparisons between upadacitinib and tocilizumab using available data and presented them in this report. EAG's analyses highlighted the possibility of differential clinical effectiveness between the two treatments. No clinical effectiveness data beyond year 1 from the trial were provided by the company, despite that such data have been collected in the second phase of the SELECT-GCA. Phase 2 of the trial was completed in March 2025. The company stated during the factual accuracy check (FAC) that this Phase 2 data is still not available but that topline data will be available in due course. It does not specify when. The company's estimation of longer-term effectiveness for upadacitinib for the key outcome of disease flare relied upon data extrapolation informed by expert opinion. The EAG examined issues surrounding the company's data extrapolation and highlighted the crucial need for data beyond year 1 to inform more reliable extrapolation. In addition,

despite that upadacitinib significantly reduced cumulative steroid use compared to placebo during year 1 of the trial, no significant differences in steroid-related adverse events were observed. While the association between cumulative exposure to steroid and its associated adverse events has been well reported in observational studies, the extent to which upadacitinib (and other steroid-sparing treatments) may reduce steroid associated adverse events remain to be demonstrated by trial evidence given the clear potential of confounding by disease severity. Evidence related to adverse events that was used in company's model was largely obtained from the literature and data collected from an observational study based on US population.

Cost-effectiveness evidence: the company created a de novo model comparing upadacitinib with 26-week steroid tapering with 52-week steroid tapering. Tocilizumab was not considered/included in the economic evaluation. The company base case assumed a patient population with the same mix of new onset and relapsing GCA patients as in the SELECT-GCA trial. A two-year stopping rule was assumed for its base case, although longer durations of treatment were also explored. Key model inputs were obtained from the year 1 data of the SELECT-GCA trial for time to first flare and time to subsequent flare. Other data were sought from the literature and from the US observational study described above. The EAG identified several errors in the company's model, all of which results in more favourable incremental cost-effectiveness ratios (ICERs) for upadacitinib. The EAG corrected these errors and presented EAG corrected company base case. The EAG further highlighted issues related to the company's assumptions related to estimation of disease flare over time, the estimated effect of upadacitinib treatment on the incidence of adverse events associated with disease flare and cumulative steroid use and the duration of impact of these adverse events, and explored their influence on estimated ICERs in EAG's base case and scenario analyses.

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1: Summary of key issues

ID6299	Summary of issue	Report sections
Issue 1	Tocilizumab was not included as a comparator. The company submission did not provide any comparative evidence between upadacitinib and tocilizumab, despite that the latter was a treatment recommended by NICE TA518 subject to a one-year stopping rule for patients with relapsing/refractory giant cell arteritis (GCA). Should tocilizumab be considered as a comparator for the relapsed subgroup, given its approval by NICE with a one year stopping rule, use within the NHS and inclusion in the assessment protocol?	1.3 5.1.3
Issue 2	No clinical effectiveness data beyond year 1 from the pivotal trial, SELECT-GCA, were presented. EAG's exploration of time to flare data limited to year 1 indicated that the data are inadequate to provide reliable, longer-term extrapolation of the key effectiveness outcome. Should the year 2 data from the main trial on times to flare be presented? The company thinks this would not be useful and also noted during factual accuracy check (FAC) that it was not available. The EAG notes that Period 2 ended March 2025. The EAG thinks that even if it would be difficult to formally incorporate into the economic modelling it would still be informative	2.5.1 5.1.2

ID6299	Summary of issue	Report sections
	in e.g. assessing whether upadacitinib use for a second year is a good use of NHS resources.	
Issue 3	Difference in clinical effectiveness between upadacitinib and tocilizumab cannot be ruled out. Preliminary adjusted indirect comparison between upadacitinib and tocilizumab indicated some possibility of difference in clinical effectiveness between treatments in favour of tocilizumab, reinforcing the need for more comprehensive assessment of relative effectiveness.	2.5.2
Issue 4	What is the relevance of the company base case? During FAC the company stated that its base case assumption of a 2 year stopping rule was just a scenario and that a stopping rule should be avoided. The cost effectiveness of upadacitinib worsens dramatically with longer stopping rules.	5.1.1
Issue 5	Multiple modelling errors identified. Multiple modelling errors, all of which led to more favourable incremental cost effectiveness ratios (ICERs) for upadacitinib, were identified by the EAG. Correcting these modelling errors worsens company base case from being dominant to an ICER of £38,359 per QALY when compared to placebo. Are the EAG corrections valid?	3.2.6.8 3.2.6.9 3.2.9.2 4.5.1
Issue 6	For the new onset subgroup should treatment sequencing be modelled Should sequencing of treatments be considered in case it is more cost effective to only use upadacitinib among those who respond poorly to steroids; i.e. at the same position as tocilizumab has been approved?	5.1.3
Issue 7	How should the time to first flare for the new onset subgroup be modelled? Is upadacitinib disease modifying or would the treatment effect wane over time once upadacitinib use has been stopped? The log-normal, Gompertz and generalized gamma result in EAG exploratory ICERs for the new onset subgroup of £42,918, £13,468 and £28,056 per QALY. If the treatment effect is	5.2.3

ID6299	Summary of issue	Report sections
	waned from year 3 over 5 years these increase to £57,296, £40,535 and £49,434 per QALY.	
Issue 8	How reliable is the company's modelling of the effects of GCA flares? The input data largely relates to incidences at diagnosis or to GCA in general. This may be a poor guide to the effect of subsequent flares.	5.2.5
Issue 9	Does the effect of steroids on risks of complications abate when off steroids? If the risks of some conditions are modelled as a function of the previous year's steroid use rather than lifetime steroid use the EAG exploratory base case worsens from £57,558 to £99,103 per QALY.	5.2.6
Issue 10	Does the modelling of steroid related conditions have face validity The incidences of steroid related conditions in SELECT-GCA at one year are typically a fraction of the company market survey incidences in the year following GCA diagnosis. Does the company modelling of steroid related conditions have face validity? Excluding this modelling worsens the EAG exploratory base case from £57,588 to £131,703 per QALY.	5.2.7
Issue 11	How often do patients visit rheumatology when tapering their steroids? The largely undocumented TA518 market survey suggests once per month. EAG expert opinion suggests most of patients, 75%, need less frequent monitoring and across all patients an average of once per two months. Other EAG expert opinion suggests a visit every three or four months, and that biologics may also need two nurse training visits. Halving monitoring costs worsens the EAG exploratory base case from £57,558 to £65,442 per QALY.	5.4.1

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Table 2: Company base case cost effectiveness estimates: Deterministic

	ITT population		New onset subgroup		Relapsed subgroup	
	Cost	QALY	Cost	QALY	Cost	QALY
Upadacitinib	████	████	████	████	████	████
Placebo	████	████	████	████	████	████
Net	████	████	████	████	████	████
ICER	Dominant		Dominant		Dominant	

The company estimates that upadacitinib provides patient benefits and saves the NHS money compared to placebo, so dominates. The company probabilistic modelling also estimates that upadacitinib dominates placebo.

1.3 The decision problem: summary of the EAG's key issues

Issue 1: Tocilizumab was not included as a comparator

Report section	1.3, 5.1.3
Description of issue and why the EAG has identified it as important	Tocilizumab, which was listed as a comparator in final NICE scope, was not included as a comparator in the company submission. Tocilizumab was recommended for treating patients with relapsing GCA with a one-year stopping rule in TA518. The absence of any comparative evidence between upadacitinib and tocilizumab in the company submission and in its response to EAG clarification questions (despite that EAG flagged up this issue) means that evidence required to inform the choice between these two treatments is lacking for patients with relapsing GCA. For patients with newly diagnosed GCA, the absence of tocilizumab related evidence in the company submission also means that the company model ignored the costs and effectiveness of an intervention that was

	recommended by NICE downstream the treatment pathway (i.e. when patients with newly diagnosed GCA experience a relapse following an initial period of remission).
What alternative approach has the EAG suggested?	EAG recognises that direct comparative evidence between upadacitinib and tocilizumab may not yet be available. Nevertheless, an adjusted indirect comparison between the two treatment options for key clinical outcomes is feasible and should be provided.
What is the expected effect on the cost-effectiveness estimates?	As tocilizumab was considered cost-effective in patients with relapsing GCA based on TA518, inclusion of tocilizumab in the modelled treatment pathway is likely to reduce the incremental QALY gain for upadacitinib compared with comparator (standard care) for patients with new onset GCA. The impact on cost-effectiveness is difficult to gauge without appropriate modelling. For patients with relapsing GCA, the potential difference in effectiveness in favour of tocilizumab cannot be ruled out based on the EAG's preliminary adjusted indirect comparison (see also Key issue 3). The effect on ICER is unknown. But it can be noted that TA518 estimated tocilizumab to have an ICER of £24,977 per QALY among relapsed patients which is less than both the EAG corrected company base case estimate of £38,359 per QALY and the EAG exploratory base case of £57,588 per QALY for upadacitinib compared to placebo.
What additional evidence or analyses might help to resolve this key issue?	For patients with new on-set GCA, scenario analyses could be undertaken to incorporate tocilizumab as one of the possible treatment options when patients experience relapse downstream. For patients with relapsing GCA, an adjusted indirect comparison of key outcomes between tocilizumab and upadacitinib could be performed, which in turn can be used to inform cost-effectiveness evaluation or cost comparison depending on the findings of adjusted indirect comparison.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2: No clinical effectiveness data beyond year 1 from the pivotal trial, SELECT-GCA, were presented

Report section	2.5.1, 5.1.2
Description of issue and why the EAG has identified it as important	EAG's exploration of time to flare data limited to year 1 indicated that the data are inadequate to provide reliable, longer-term extrapolation of the key effectiveness outcome. Should the year 2 data from the main trial on times to flare be presented? The company thinks this would not be useful. The EAG thinks that even if it would be difficult to formally incorporate into the economic modelling it would still be informative in e.g. assessing whether upadacitinib use for a second year is a good use of NHS resources.
What alternative approach has the EAG suggested?	Presentation of Period 2 Kaplan Meier data on time to first flare and time to subsequent flare separately for each of the Period 2 patient splits. Period 2 ended in March 2025. The company notes that this data is not available but that topline data will be, though does not state when.
What is the expected effect on the cost-effectiveness estimates?	This is unknown, but additional data beyond year one will allow the choice of curves for extrapolating long-term effectiveness to be guided by some empirical evidence rather than purely based on clinical opinion. A better assessment of the likely cost effectiveness the effect of a 1 year stopping rule compared to a 2 year stopping rule would also be possible.
What additional evidence or analyses might help to resolve this key issue?	Period 2 Kaplan Meier data on time to first flare and time to subsequent flare separately for each of the Period 2 patient splits as requested in EAG clarification question A15.

Issue 3: Difference in clinical effectiveness between upadacitinib and tocilizumab cannot be ruled out.

Report section	2.5.2
Description of issue and why the EAG has identified it as important	Preliminary adjusted indirect comparison between upadacitinib and tocilizumab indicated some possibility of difference in clinical effectiveness between the treatments in favour of tocilizumab, reinforcing the need for more comprehensive assessment of relative effectiveness.
What alternative approach has the EAG suggested?	In the absence of direct comparative evidence, the company could undertake adjusted indirect comparison to provide estimates for relative effectiveness for upadacitinib compared with tocilizumab for patients with relapse/refractory disease. Such effect estimates, such as hazard ratios for time to flare, could then be incorporated into its economic modelling.
What is the expected effect on the cost-effectiveness estimates?	This is unknown. But it can be noted that TA518 estimated tocilizumab to have an ICER of £24,977 per QALY among relapsed patients which is less than the EAG corrected company base case estimate of £38,359 per QALY for upadacitinib compared to placebo.
What additional evidence or analyses might help to resolve this key issue?	Major model revisions to permit the sequencing of treatments to be explored. This can be informed by adjusted indirect comparison of clinical effectiveness data.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 4: What is the relevance of the company base case economic modelling?

Report section	5.1.1
Description of issue and why the EAG has identified it as important	The company base case applies an upadacitinib two year stopping rule. During FAC the company stated that it “models a two-year treatment duration as a scenario” alongside a “variety of scenario analysis evaluating the cost-effectiveness of different treatment durations” and that “A stopping rule would prevent upadacitinib providing such a flexible treatment for patients and should be avoided.”

What alternative approach has the EAG suggested?	This arose during FAC so the EAG has not been able to address this other than through scenario analyses around the stopping rule.
What is the expected effect on the cost-effectiveness estimates?	The longer the treatment duration of upadacitinib the worse its cost effectiveness. The EAG revised base case ICERs for different stopping rules for the ITT modelling are: • 1 year £35,371 per QALY • 2 years £57,558 per QALY • 3 years £74,825 per QALY • 5 years £100,612 per QALY • No stopping rule £150,381 per QALY
What additional evidence or analyses might help to resolve this key issue?	Modelling of upadacitinib discontinuations rates in the absence of a stopping rule.

Issue 5: Multiple modelling errors identified

Report section	3.2.6.8, 3.2.6.9, 3.2.9.2, 4.5.1
Description of issue and why the EAG has identified it as important	The EAG has identified 7 errors in the company model. These all increase the estimated ICERs for upadacitinib. Are the EAG model corrections valid?
What alternative approach has the EAG suggested?	Correcting the modelling errors.
What is the expected effect on the cost-effectiveness estimates?	For the ITT population upadacitinib is no longer dominant. The EAG corrected company base case has an ICER of £38,359 per QALY.
What additional evidence or analyses might help to resolve this key issue?	None.

Issue 6: For the new onset subgroup should treatment sequencing be modelled?

Report section	5.1.3
Description of issue and why the EAG has identified it as important	For the new onset subgroup the company only compares upadacitinib use and 26-week steroid tapering with placebo and 52-week steroid tapering. It does not consider using tocilizumab upon relapse in the placebo arm. It also does not consider using upadacitinib upon relapse in the placebo arm. Reserving the more expensive treatments for those who do poorly with steroids and relapse may be more cost effective than treating all patients with the more expensive treatments.
What alternative approach has the EAG suggested?	Consideration of the sequencing of treatments. This is likely to require major model revisions.
What is the expected effect on the cost-effectiveness estimates?	This is unknown.
What additional evidence or analyses might help to resolve this key issue?	Major model revisions to permit the sequencing of treatments to be explored.

Issue 7: How should time to first flare be modelled for the new onset subgroup?

Report section	5.2.3
Description of issue and why the EAG has identified it as important	The company base case selects the Gompertz curves without waning the treatment effect after cessation of upadacitinib use. These plateau from year three causing the model to estimate that ■ more patients in the upadacitinib arm will avoid flaring in perpetuity. The company advisory board suggests that

	EAG expert opinion is that upadacitinib is unlikely to be disease modifying so when stopped at 2 years the upadacitinib curve will converge towards the placebo curve. The TA518 FAD expert opinion suggests that the Gompertz is perhaps too optimistic and the log-normal too pessimistic when modelling the placebo arm at 3 to 5 years. It also suggests that the Gompertz is too optimistic and the log-normal is about right at 10 years. The Gompertz for the new onset coupled with the relapsed modelling yields weighted averages that are inconsistent with the ITT modelling.
What alternative approach has the EAG suggested ?	Using the log-normal, and exploring the Gompertz and the Generalised gamma coupled with waning the treatment effect.
What is the expected effect on the cost-effectiveness estimates ?	For the new onset subgroup the EAG exploratory base case ICER is £42,918, £13,468 and £28,056 per QALY using the log-normal, the Gompertz and the generalised gamma respectively. Treatment waning over 5 years increases these to £57,296, £40,535 and £49,434 per QALY respectively.
What additional evidence or analyses might help to resolve this key issue?	Further expert opinion on whether upadacitinib is disease modifying with a permanent reduction in flares after treatment cessation or if there would be a waning of the treatment effect.

Issue 8: Is the modelling of GCA flare related complications accurate?

Report section	5.2.5
Description of issue and why the EAG has identified it as important	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. EAG expert opinion is that rates of complications at presentation are somewhat higher than at subsequent flares due to diagnosing preexisting conditions, the conditions being the reason for presentation and patients being better controlled and better educated by the time of any subsequent flares.
What alternative approach has the EAG suggested?	Scenario analyses around the rates of GCA flare related complications.
What is the expected effect on the cost-effectiveness estimates?	For the ITT population the EAG exploratory base case ICER worsens from £57,558 to £60,972 per QALY if major stroke is 50% of the base case, and to £62,848 if major stroke is 25% of the base case.
What additional evidence or analyses might help to resolve this key issue?	Rates of complications associated with flares among relapsing patients during Period 1 of SELECT-GCA, and if available from the literature.

Issue 9: Does the effect of steroids on risk of complications abate when off steroids?

Report section	5.2.6
Description of issue and why the EAG has identified it as important	The company model assumes that the risks of developing conditions that are exacerbated by steroid use is a function of the total cumulative steroid use to date. EAG expert opinion is that the risks of developing some conditions will abate when steroid use is stopped. During FAC the company highlighted two papers that suggest the increased risk of developing diabetes and the increased risk of infection due to steroid use rapidly abates after cessation of steroids back to or close to the original baseline risk.

What alternative approach has the EAG suggested?	Exploring modelling the risks of some events being determined by the average steroid dose in the preceding year.
What is the expected effect on the cost-effectiveness estimates?	For the ITT population the EAG exploratory base case ICER worsens from £57,558 to £99,103 per QALY.
What additional evidence or analyses might help to resolve this key issue?	It is unclear whether a reanalysis of the data from the US health insurance database can address this.

Issue 10: Does the modelling of steroid related conditions have face validity?

Report section	5.2.7
Description of issue and why the EAG has identified it as important	The company model inputs of annual incidences of conditions exacerbated by steroid use bears no relation to the observed incidences in the SELECT-GCA placebo arm at one year. The model annual incidences are derived from an analysis of a US Health Insurance database data on GCA patients in the year after their diagnosis so should be aligned with SELECT-GCA data for the new onset subgroup. The modelled annual incidences are typically large multiples of the SELECT-GCA ITT population incidences.
What alternative approach has the EAG suggested?	Removing the modelling of steroid related conditions as the EAG thinks it lacks face validity. This is not to say that upadacitinib does not have a steroid sparing effect or that this will not result in cost offsets and patient benefits.
What is the expected effect on the cost-effectiveness estimates?	For the ITT population the EAG exploratory base case ICER worsens from £57,558 to £131,703 per QALY.
What additional evidence or analyses might help to resolve this key issue?	It is unclear whether a reanalysis of the data from the US health insurance database can yield sensible estimates for model inputs.

Issue 11: How often do patients visit rheumatology when tapering their steroids?

Report section	5.4.1
Description of issue and why the EAG has identified it as important	The company uses estimates from TA518, which are based upon a market survey conducted by the TA518 company. No details of the market survey method are presented in either the TA518 company submission or EAG report, with only the final resource use estimates being presented. The survey suggests roughly monthly patients visits to rheumatology outpatients when tapering steroids. EAG expert opinion is that 75% of patients manage with fewer visits, the remainder being roughly equally split between those requiring slightly more visits than the 75% and those requiring monthly visits. This translates into roughly a visit every other month when tapering steroids. Other EAG expert opinion suggests a visit every three or four months, and that biologics may also need two nurse training visits.
What alternative approach has the EAG suggested?	A scenario analysis that halves the ongoing monitoring costs. Note that while rheumatology visits are the main cost driver, this also halves the other elements of monitoring costs such as visits to geriatricians.
What is the expected effect on the cost-effectiveness estimates?	The EAG exploratory base case for the ITT population worsens from £57,558 to £65,442 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Further expert opinion on the frequency of visits during initial steroid tapering and after successfully completing steroid tapering.

1.6 Other key issues: summary of the EAG's view

None

1.7 Summary of EAG's preferred assumptions and resulting ICER

The EAG applies a number of corrections to the company base case as outlined in section 4.5.1 and as summarised in Table 3 below.

- **Error 01:** Not taking into account baseline cumulative steroid use.

- **Error 02:** Only those on steroids have a risk of conditions whose incidence can be exacerbated by steroid use.
- **Error 03:** The calculation of the incidences of permanent conditions does not take into account their prevalences.
- **Error 04:** The conversion of annual incidences to weekly incidences is based upon a survivor analysis rather than dividing the annual incidence by 52.
- **Error 05:** The 26 week tapering period is retained in the upadacitinib arm after upadacitinib is stopped at 2 years, rather than switching to the 52 week tapering period.
- **Error 06:** Not conditioning the mean steroid dose for a model cycle by the proportion surviving.
- **Error 07:** Not weighting the cost of prednisolone by market share.

Table 3: EAG corrections to company base case

	Section	Δ Cost	Δ QALY	ICER
Company base case	4.2	████	████	Dom
Error 01: Baseline total steroid dose	3.2.3	████	████	Dom
Error 02: Cohort risks of conditions	3.2.6.8	████	████	Dom
Error 03: Condition prevalences	3.2.6.8	████	████	Dom
Error 04: Condition incidences	3.2.6.8	████	████	Dom
Error 05: Placebo tapering off Tx	3.2.6.9	████	████	Dom
Error 06: Steroids used cond. by OS	3.2.6.9	████	████	Dom
Error 07: Prednisolone cost	3.2.9.2	████	████	Dom
EAG corrected company base case	..	████	████	£38,359

Probabilistic modelling provides a central estimate of £42,863 per QALY.

The EAG makes the following changes to the company base case.

- EAG01: Correcting the model errors as summarised above.
- EAG02: A baseline age of 73 years

- EAG03: Log-normal time to first flare among the new onset subgroup
- EAG04: Revising the duration of the quality of life effect of some of the transient events to be less than one year
- EAG05: Applying EAG estimates of the costs of some events
- EAG06: Minor issues, this also 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.

Table 4: EAG changes: pairwise cost effectiveness estimates vs placebo

	Section	ITT	New onset	Relapsed
EAG01: Model corrections	4.5.1	£38,359	£4,614	£70,797
EAG02: Baseline age 73 years	5.2.1	£38,725	£6,096	£69,414
EAG03: Log-normal time to first flare	5.2.2	..	£23,344	..
EAG04: Transient QoL durations	5.3.2	£46,147	£5,415	£86,560
EAG05: Event costs	5.4.2	£44,129	£8,138	£78,787
EAG06: Minor issues	5.5	£41,206	£6,192	£70,576
EAG base case: EAG01-EAG06	..	£57,558	£42,918	£98,754

External Assessment Group Report

1 INTRODUCTION AND BACKGROUND

1.1 Introduction

This EAG report has been prepared to critique and appraise the clinical effectiveness and cost-effectiveness evidence of upadacitinib (RINVOQ®) for the treatment of giant cell arteritis (GCA) in adult patients within its marketing authorisation. The company submission (CS) provided by AbbVie to NICE stated that a type II variation application to extend the therapeutic indication by including treatment for GCA was submitted to the Medicines & Healthcare products Regulatory Agency (MHRA) on 21 March 2025 under the International Recognition Procedure (IRP) (CS Document B, Section 1.1 and Section 1.2, Table 2). It was also reported that the Committee for Medicinal Products for Human Use (CHMP) had given positive opinion on 27 February 2025 and the type II variation application for the GCA indication was granted by the European Commission on 7 April 2025 (CS Document B, Section 1.1).

1.2 Background

The company provided a comprehensive description of the relevant health condition (GCA) along with the current treatment pathway for GCA in CS Section 1.3.1 and 1.3.2. Additionally, a brief description of upadacitinib and its potential positioning in the treatment pathway is provided in CS Section 1.3.4. The EAG, in consultation with the clinical advisor, has reviewed this evidence and found the company's rationale for positioning upadacitinib for the management of GCA to be generally appropriate and justifiable.

1.2.1 Condition, symptoms and economic burden

GCA is a chronic, immune-mediated vasculitis characterised by granulomatous inflammation of medium and large sized arteries, resulting in vascular remodelling and impaired blood flow.¹ The inflammatory process involves release of cytokines

which drives T cells differentiation and activates macrophages leading to unmanaged inflammation and subsequent vascular damage.^{2, 3}

The condition predominantly affects individuals aged >50 years, with women aged 70–79 experiencing a 2–3-fold higher incidence than men.^{4, 5} It is also the most common form of vasculitis in the Western world and primarily affects individuals of Caucasian descent, particularly those of Northern European or Scandinavian origin.^{1, 6} In the UK, the incidence is approximately 2.2 per 10,000 person-years, with 94.3% being white British or Irish.^{5, 7} There is also regional variation exists within the UK, with highest incidence observed in the South and East England, and lower rates in Scotland.⁵

The clinical presentation of GCA varies with the location of the affected vessels with the large arteries of head and neck most frequently involved.⁸ Common cranial GCA symptoms include temporal artery thickening, lack of pulse, scalp tenderness, jaw claudication, tongue oedema or necrosis, along with systemic features such as malaise, anorexia, fever, and weight loss.^{1, 4, 8, 9} A major complication of cranial GCA is vision loss due to ischemia of ophthalmic artery. It is reported that up to one third of patients experience vision impairment, with permanent vision loss occurring in approximately 17% of patients.^{1, 10-13} The extracranial GCA often affects the aorta leading to cardiac complications such as aortic aneurysm and stroke.^{9, 14-16} Due to these risks, GCA is considered a medical emergency.^{10, 12} GCA also shares clinical features with polymyalgia rheumatica (PMR), which coexists in approximately 40–60% of patients.¹⁷⁻¹⁹ Additionally, diagnosis often requires imaging such as ultrasonography, magnetic resonance angiography (MRA), computed tomography angiography (CTA), or positron emission tomography (PET).²⁰ However, these investigations are not consistently used in routine clinical practice, and as a result a significant proportion of arterial involvement may remain undiagnosed according to clinical advice received by the EAG.

High dose corticosteroids are used in the initial treatment to control symptoms, reduce inflammation, and minimise the risk for complications.^{9, 14, 21, 22} Achieving sustained, steroid-free remission is key treatment goal for GCA. However, disease relapse or flare-ups are common and imposes a significant burden on patient.^{10, 12, 23-}

²⁵ The European Alliance of Associations for Rheumatology (EULAR) classifies

relapses as major or minor, based on symptom severity, and provides corresponding treatment guidelines. However, the EAG clinical advisor highlighted that the severity of major relapse may not always be captured by the routine investigations and may require advanced imaging. Additionally, minor relapse may progress to major relapse, potentially causing organ damage.

Relapses contribute to long-term complications, increased anxiety, and a reduced quality of life.^{26, 27} Management of relapses typically involves increasing corticosteroid doses and extending treatment duration, which further suppresses the immune system. This prolonged corticosteroid use is associated with a wide range of adverse effects (AEs), some of which are irreversible and may increase the risk of morbidity and mortality. Common conditions associated with corticosteroid use include hypertension, type 2 diabetes mellitus, osteoporosis, and heart failure.²⁸⁻³² Rapid progression of osteoporosis induced by corticosteroids can have significant impact on patient's life. These cumulative health changes may also be associated with mental wellbeing, increased all-cause mortality and often have impact that extends beyond the patient.

The management of GCA imposes a considerable and long-term burden on healthcare systems due to extensive inpatient, outpatient, and pharmaceutical resource use.^{33, 34} In Europe, costs reach €4,005 in the first 18 months and €7,236 over five years, largely due to healthcare utilisation.³⁵ Together, GCA and its complications pose a significant economic burden to patients and the healthcare systems.³⁴

1.2.2 Clinical pathway and unmet needs

Relevant treatment guidelines are published by the British Society for Rheumatology (BSR) and EULAR.^{10, 12} Both recommend initiating high-dose corticosteroid therapy (40–60 mg/day) immediately upon suspicion of GCA, followed by gradual tapering to ≤5 mg/day over 18–24 months. BSR suggests a tapering period of 12-18 months, whereas EULAR promotes a faster tapering approach.^{10, 12} In routine clinical practice, however, tapering often takes up to two years.

Despite treatment, relapse rates remain high. One meta-analysis reported a 3.3% incidence of major relapse in newly diagnosed patients²⁴ while another meta-

analysis found overall prevalence of 47.2% (95% CI 40.0, 54.3) among patients treated with glucocorticoids.³⁶ Such relapses typically require either an increase in corticosteroid dosage or a slower tapering schedule.³⁷ For major relapses, both BSR and EULAR guidelines recommend restarting high-dose corticosteroids; for minor relapses, an increase to the previous higher dose is advised. This often leads to high cumulative steroid exposure and associated AEs.^{10, 12}

For adults with relapsing or refractory GCA, NICE technology appraisal TA518 recommends weekly tocilizumab, administered via subcutaneous injection alongside corticosteroid tapering (and may continue after completion of the tapering) for up to one year.³⁸ However, challenges remain regarding its accessibility particularly beyond major treatment centres, and acceptability among elderly patients. There is also continued risk of relapse.^{39, 40} As it can take several weeks or months for tocilizumab to take effect, concurrent corticosteroid use is necessary during the initial treatment phase. This overlap can sometimes exacerbate adverse effect symptoms or lead to unrecognised side effects.

While guidelines mentioned off-label use of conventional immunosuppressants such as leflunomide and methotrexate as adjunctive therapies, their application in clinical practice is inconsistent and is only supported by limited evidence.

Given the limitations of current treatment options including high relapse rates and corticosteroid-related adverse events, there remains a significant unmet need for long-term, effective, and well-tolerated corticosteroid-sparing treatments.

1.2.3 Positioning of upadacitinib

Upadacitinib is a small molecule, reversible JAK inhibitor which acts upon the two key cytokines, interferon- γ (IFN- γ) and interleukin-6 (IL-6), that are responsible for driving inflammation in GCA. The company has positioned upadacitinib for use during the corticosteroid tapering phase in adults, both in newly diagnosed GCA patients and in those with relapsing/refractory disease. CS Document B, Section 1.3.4.2 provides the company's rationale for positioning of upadacitinib in the clinical pathway. The proposed positioning is in line with NICE's final scope.

1.3 Critique of company's definition of decision problem

EAG's critique of company's definition of decision problem is provided in Table 5 below. EAG considers the exclusion of tocilizumab, a treatment recommended for relapsing/refractory GCA in TA518 subject to a one-year stopping rule, as a crucial omission in CS that is not justified by the reasons put forward by the company (see details below).

Table 5: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with giant cell arteritis	As per NICE scope	Not applicable	The population specified in the company decision problem essentially covers the whole population of adults with GCA, which is in line with final NICE scope. The patient population in the SELECT-GCA trial may be slightly younger but is broadly similar to the patient population eligible for treatment in England and Wales.
Intervention	Upadacitinib	As per NICE scope	Not applicable	NICE scope and the company submission are in line with the anticipated marketing authorisation for upadacitinib.
Comparator(s)	• Tapering course of corticosteroids • Tocilizumab in combination with a tapering course of corticosteroids, or alone if used after corticosteroids • Methotrexate in combination with a tapering course of corticosteroids	• Tapering course of corticosteroids	The company submission only included one of the three comparators listed in the final NICE scope. The company offered the following justifications: “The population considered in the submission is adults with GCA. The main treatment option for GCA is a tapering course of steroids. However, due to the chronic, relapsing and remitting nature of GCA, patients can require repeated and long-term treatment. Corticosteroids are considered the appropriate comparator for this appraisal given upadacitinib covers	EAG considered the exclusion of tocilizumab (used in combination with a tapering course of corticosteroids, or alone when used after corticosteroids) as a key omission in the company submission. The company cited two main reasons in their justifications: (1) tocilizumab treatment is restricted to one-year duration in relapsing GCA patients only (based on NICE TA518). (2) the restriction in treatment duration as specified in TA518 has led to limited and lower

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			the same patient population and is intended as a flexible long-term treatment option for patients. Following insights from clinical experts, tocilizumab is not considered a relevant comparator for the following reasons: 1. Tocilizumab has a restrictive fixed one-year treatment duration and is recommended in relapsing GCA patients only. After treatment, relapse rates are high, and patients are forced to return to back to corticosteroids. As such it is considered a short-term treatment, and often further reserved for patients with an increased risk of corticosteroids related AEs. 2. Additionally, clinicians reported that the implementation of the treatment duration restrictions have led to access challenges with tocilizumab, leading to its limited use. The administrative hurdles, including the requirement for Blueteq authorisation and the need for multi-disciplinary team alignment, create barriers in accessing tocilizumab for time-sensitive cases. This situation	than anticipated use of tocilizumab in the NHS. The EAG disagrees. Point (1) above specifies the use of tocilizumab in a patient subgroup in the treatment pathway of GCA covered by the anticipated marketing authorisation for upadacitinib, and therefore justifies the <i>inclusion</i> of tocilizumab as a comparator. Point (2) above describes issues in the uptake of tocilizumab in clinical practice, which may reflect administrative and logistic barriers under current service delivery arrangement in the NHS, as well as patient preference. These practical issues do not preclude tocilizumab being a potential treatment alternative and hence a suitable comparator. The company also provided two main reasons as the justifications for excluding methotrexate as a comparator in the company submission: (1) Methotrexate is used as an adjunctive therapy and its use is varied and largely at clinician's discretion. (2) Evidence on the effectiveness of methotrexate in GCA is limited and inconclusive, and therefore it is not considered an

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			often leads clinicians to revert to corticosteroid treatment to rapidly manage relapses. These challenges are further echoed in a recent report by the Getting It Right First Time (GIRFT) NHS programme, which reported use of tocilizumab as lower than anticipated due to the additional bureaucracy associated with access. Additionally, methotrexate is not considered a relevant comparator for the following reasons: 1. Consultation with clinicians has emphasised the varied use of methotrexate as an adjunctive therapy across UK clinical practice. Methotrexate is used according to clinician discretion due to the lack of available alternate treatments and clinician familiarity with methotrexate, with its benefits uncertain due to limited evidence. 2. Due to uncertainty regarding the effectiveness of methotrexate, it is not regarded as an established treatment option. Evidence is derived from three small, double-blind, placebo-controlled trials,	established treatment option for GCA. The EAG, having consulted its clinical advisers, agreed with the justifications provided by the company and hence the exclusion of methotrexate as a comparator.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			however, meta-analyses of these trials have found contradictory results concerning the effectiveness of methotrexate in GCA. Therefore, corticosteroids are deemed the only relevant comparator in UK clinical practice for this submission in the population adult patients with GCA, as supported by clinical expert opinion. This comparator is addressed in the company's decision problem and aligns directly with the specification in the NICE scope."	
Outcomes	The outcome measures to be considered include: • disease remission • time to relapse after disease remission • cumulative dose of corticosteroids • adverse effects of long-term corticosteroid treatment (including weight gain, osteoporotic	As per NICE scope	Not applicable	Outcomes covered by the company submission are consistent with the final NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	fractures, hypertension, cataracts, cardiovascular events, mood disturbance and diabetes mellitus) • morbidity (including vision loss, stroke and aortic aneurysm) • mortality • adverse effects of treatment (including thromboembolism) • health-related quality of life.			
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	As per NICE scope	Not applicable	As the company did not include tocilizumab as a comparator in their submission, the cost-effectiveness of upadacitinib in comparison with tocilizumab in the patient population eligible for the latter treatment was not evaluated. EAG considers this as a major omission in the company submission as highlighted above. A biosimilar for tocilizumab is available in the UK and its cost is considered

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	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 and cost of biosimilar and generic products should be taken into account.			in separate analyses presented in EAG report's cPAS appendix. ⁴¹
Subgroups	If the evidence allows the following subgroups will be considered: • People with newly diagnosed giant cell arteritis • People with relapsing giant cell arteritis • People who have experienced previous	Not clearly described.	The company offered the following explanation for their approaches: “The population considered in the company submission are adult patients with GCA, aligned to the anticipated marketing authorisation and the NICE scope. However, for completeness, subgroup analyses in newly diagnosed and relapsing GCA subgroups are provided in CS Appendix C. The following subgroups are not considered separately explicitly but rather captured within the defined	The company submission covered the whole adult population with GCA. The clinical effectiveness evidence was mainly based on the SELECT-GCA trial, in which two-thirds of participants had newly diagnosed GCA and one-third had relapsing GCA. The company's base case was based on this mixed population. Subgroup analyses separately evaluating new on-set and relapsing population were only described briefly in CS Appendix C.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	corticosteroid toxicity or have pre-existing conditions likely to be exacerbated by corticosteroids • People who have had up to 12 months of tocilizumab • People for whom tocilizumab is unsuitable		population of adult patients with GCA. 1. People who are unsuitable to corticosteroids: Consultation with UK clinicians emphasised that patients with prior corticosteroid toxicity will still receive corticosteroids in clinical practice to control disease relapse given the lack of alternative treatment options and risk of serious GCA related complications without treatment. Clinicians did not deem this as a clinically distinct subgroup. 2. People who have had up to 12 months of tocilizumab & people unsuitable to tocilizumab: Similarly, it is understood that patients who are unsuitable for tocilizumab, or following tocilizumab completion would also receive corticosteroids in clinical practice. This submission provides a relevant comparison to corticosteroids as discussed. “	The company's subgroup analyses for relapsing population used a tapering course of corticosteroid as the comparator and thus ignored tocilizumab recommended by NICE in TA518. The EAG agrees that the other three subgroups listed in the final NICE scope, i.e. people who have experienced previous corticosteroid toxicity or have pre-existing conditions likely to be exacerbated by corticosteroids, people who have had up to 12 months of tocilizumab, and people for whom tocilizumab is unsuitable, are broadly covered by the assessment of whole GCA population and may not warrant a separate assessment.
Special considerations including issues	Guidance will only be issued in accordance with the marketing	Not clearly described.	Not applicable.	None.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
related to equity or equality	authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.			

2 CLINICAL EFFECTIVENESS

2.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify evidence for the efficacy and safety of interventions for the treatment of GCA, described in CS Appendix B. The SLR was conducted following the CRD's guideline for systematic reviews, the Cochrane Handbook for Systematic Reviews, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and requirements set out by NICE.⁴²⁻⁴⁵

The EAG completed the modified ROBIS risk of bias assessment reported in Appendix 2 and summarised in Table 6.⁴⁶ Overall, the EAG judged the risk of bias in the company's SLR to be of 'some concerns', with 'low concern' in two domains and 'some concerns' in the remaining two. A more detailed critique from the EAG is reported in the sections that follow.

Table 6: Summary of the EAG's critique of the company's SLR

Domain	Section(s) of CS assessed	EAG overall assessment
Study eligibility criteria	CS Appendix B (Page no 16), Table 11 and Table 12	Low concern
Identification and selection of studies	CS Appendix B (Page no 24), Figure 1 and Figure 2. CS Appendix B (Page no 53), and Table 25.	Some concern
Data collection and study appraisal sections	CS Appendix B (Page no 19), and Table 13 CS Appendix B (Page no 161), and Table 29 CS Appendix B (Page no 167), Table 30 to Table 46	Low concern
Synthesis and findings	CS Document B, Section 2.1 and Section 2.2	Some concern

2.1.1 Searches

A broad and appropriate range of bibliographic databases, clinical trials registries and proceedings of recent conferences were searched on the 3rd of April 2024, and updated on the 18th February 2025. The searches reported in CS Appendix B Tables 1-8 include database-specific indexing and free text terms and do not include date or language restrictions. However, the EAG notes several methodological issues that could potentially raise questions regarding the completeness of the company's approach. Firstly, the search terms for corticosteroids could be broadened to include search terms for 'Methotrexate' and 'tapering'. Secondly, whilst reasonably comprehensive search filters were used to restrict to the RCTs and primary studies, the EAG notes that the search terms for systematic reviews are somewhat limited and did not include search terms for ITCs. The EAG ran a targeted search for systematic reviews and meta-analyses and large-scale observational studies (Appendix 1: EAG searches). Results of the targeted searches are being reviewed by the EAG to ascertain whether potentially useful data/studies have been missed by the company. Thirdly, the Medline, Embase and PubMed searches were restricted using the in-built filter for humans, which is not in line with Cochrane handbook recommendation, which recommends the validated double NOT method of 'Humans/ Not animals' (CS Appendix B Tables, 1, 2 and 8).⁴⁷ Applying this limit may remove potentially relevant studies as it would exclude any papers which do not have the Humans thesaurus/ Subject Heading assigned to them. Most significantly, the EAG notes that the Medline, Embase and PubMed searches include a search strand that appears to be related to the outcomes reported in the decision problem (CS Table 1), including: 'remission', 'adverse events' and 'the 36 item Short Form Quality of Life', which is combined with the search terms for population and intervention and study types (CS Appendix B Table 1 Table 2 and Table 8). The EAG notes that since the decision problem does not restrict the population to being: at late stage, in remission, experiencing adverse effects or undergoing a tapering course of corticosteroids, restricting the search strategy in this way considerably reduces the sensitivity and increases the risk of removing potentially relevant studies. The EAG carried out a revised search that did not include these terms (see Appendix 1: EAG searches), which retrieved 1831 de-duplicated results. This raises major concerns regarding the completeness of the search strategy. This is further discussed in Section 2.1.7.

Searches for the condition only were carried out on a broad range relevant clinical trial registries and conference websites and the numbers of included results are reported (CS Appendix B Tables 9 and 10). Additionally, the EAG notes that the company reports the list of systematic reviews from which reference checks were conducted; however, the EAG does not cross check the accuracy.

2.1.2 Inclusion criteria

The CS Appendix B, Table 11 and Table 12 outlined the inclusion and exclusion criteria used to screen the retrieved records. The Population, Interventions, Comparators, Outcomes, and Study design (PICOS) framework was used to guide the screening process. The EAG noted that the initial screening employed broader eligibility criteria (CS Table 11) and the full-text articles, that meets this broader eligibility criteria were reassessed using more focused eligibility criteria (CS Table 12). The company reported that the focused criteria (CS Table 12) were also used to identify relevant studies for data synthesis. Under this criterion, the study designs were restricted to phase 2 and 3 randomised controlled studies only. In addition, the outcome measures were aligned with those used in the SELECT-GCA trial. The company didn't provide justification to for the narrowed focus on specific outcomes which raises concern to the EAG about potential exclusion of relevant studies.

The EAG further observed that beyond study design and outcomes, the eligibility criteria in CS Table 12 also limited comparators to corticosteroids and other directly comparable interventions.

2.1.3 Selection of the included studies

The company provided description of the study selection process in CS Appendix B (Page 24), Figure 1 and Figure 2. Selection of studies was undertaken in two phases: (a) reviewing of abstracts and full text based on broad PICOS criteria reported in CS Appendix B, Table 11 and (b) further screening of studies identified in the first phase using a more focused PICOS framework reported in CS Appendix B, Table 12. Both phases of screening were conducted by two reviewers independently, with any discrepancies resolved by a third reviewer.

The company reported that 343 studies were retrieved through initial search and an additional 28 studies were identified during the updated search. Of these 371

records, 14 reports presenting four studies were included in the clinical evidence synthesis. The list of eligible studies was described in CS Appendix B, Table 47. The list of excluded studies along with reasons for exclusion was reported in CS Appendix B, Table 49. However, due to limited time available, the EAG did not verify the accuracy of all study exclusions. Instead, the EAG focused on the studies published between 2020 and 2025 and agrees with the exclusion of those studies.

In addition to the clinical evidence, the company reported an additional 37 reports corresponding to 33 observational studies that report adverse event data among GCA patients receiving glucocorticoids. The evidence from these observational studies was used to estimate the incidence of glucocorticoid related adverse events. The list of eligible studies and their characteristics was described in CS Appendix B, Table 25. However, the company did not explicitly describe the methodology used to identify these 37 additional reports which raised concern to the EAG regarding the transparency of the selection process.

2.1.4 Critique of data extraction

CS Appendix B, Page 19 and Table 13 summarises the data extraction process and the items extracted. The EAG noted that the company adopted an appropriate approach to data extraction with two reviewers independently extracting data using a standardised form. Any discrepancies between the two reviewers were resolved by consensus or by involving a third researcher.

2.1.5 Quality assessment

The EAG finds company's approach to critical appraisal appropriate, noting that two reviewers independently appraised the studies and any disagreements resolved by involving a third reviewer. CS Appendix B, Page no 161 and Table 29 reported quality appraisal for the selected RCTs using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2).^{48, 49}

The EAG separately assessed the quality of the included study using the RoB2.⁴⁹ The complete assessment is reported in CS Appendix A Table 70 and a critique of company's assessment is reported in Section 2.2.2 below.

In addition, the company has also critically appraised selected observational studies, using the Cochrane "Risk Of Bias In Non-randomised Studies – of Interventions" tool (ROBINS-I, Version of 12 October 2016).⁴⁸ The company reported the full assessment in CS Appendix B (Page no 167), Table 30 to Table 46. As these studies are not included in the evidence synthesis, the EAG did not undertake further appraisal or verify the accuracy of the company's assessments.

2.1.6 Evidence synthesis

The company provided narrative descriptions and summary tables in CS Appendix B. Overall, the company identified, four individual trials evaluating the effectiveness of upadacitinib (SELECT-GCA), tocilizumab (GiACTA), secukinumab (TitAIN) and abatacept (ABA). Of these, only upadacitinib and tocilizumab were included in the NICE scope for this technology appraisal. Although relevant comparator, tocilizumab, was identified, only the SELECT-GCA trial, was used to inform clinical effectiveness. Moreover, the company didn't perform an indirect comparison with the relevant comparator, tocilizumab, which raises concern to the EAG regarding the reported evidence in the CS Document B Section 2. This is further critiqued in Section 2.2.

In addition, the company reported evidence from a retrospective observational real-world evidence study (RWE) conducted to assess patient characteristics, economic burden, treatment pattern and AEs associated with corticosteroids use.⁵⁰ However, the methodology used to identify and select this study was not explicitly outlined in CS Appendix B. Furthermore, this RWE study was not listed among the included observational studies presented in CS Appendix B, Table 25. There was therefore a disconnection between the company's SLRs and the evidence that was used to inform the company's economic modelling.

2.1.7 Additional work on SLR undertaken by the EAG

The revised search (**Appendix 1: EAG searches**) conducted by the EAG identified 1,831 unique records which were screened by a single reviewer using the eligibility criteria reported in CS Appendix B, Table 11. Additionally, the EAG identified two recent systematic reviews,^{51, 52} the reference list of which were screened for relevant studies. This search identified additional eight trials evaluating the safety and efficacy of five different drugs including mavrilimumab, adalimumab, methotrexate,⁵³⁻⁵⁵ infliximab,⁵⁶ and sirukumab.^{57, 58} Four of these drugs fall outside of NICE scope for current appraisal, thus they were not considered further.

When applying the more focused criteria, outlined in CS Appendix B, Table 12, studies evaluating methotrexate^{53-55, 59} were deemed relevant to include. However, the EAG agrees to company's rationale to exclude methotrexate from the treatment comparison. As a result, these studies appeared not relevant for further inclusion in the SLR. Notably, this additional search conducted by EAG, did not retrieve RWE study.⁵⁰ These further points out the methodological accuracy and comprehensiveness of company's search strategy.

Overall, the company took a reasonably systematic approach to identifying potentially relevant studies and extracting data from them in the SLR. However, only a single trial conducted by AbbVie was ultimately included in the CS, representing two included reports from the SLR and used to inform the clinical effectiveness. No synthesis of other data was performed.

2.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The clinical evidence presented in the CS for the efficacy and safety of upadacitinib in patients with GCA was obtained from two data sources:

- SELECT-GCA: A phase 3, randomised, double-blind, placebo-controlled, multicentre trial and
- A real-world evidence study (RWE) conducted to derive patient characteristics, economic burden, treatment patterns, and burden of corticosteroid-related adverse events (AEs).

2.2.1 SELECT-GCA

The SELECT-GCA trial evaluated the efficacy and safety of upadacitinib in adult patients ≥ 50 years with active new onset or relapsing GCA.^{60, 61} The trial comprised a 52-week double blind placebo-controlled phase (Period 1) and a 52-week blinded extension (Period 2). In Period 1, patients were randomised in a 2:1:1 ratio to receive upadacitinib 15 mg + 26-week corticosteroid (CS) taper regimen, upadacitinib 7.5 mg + 26-week CS taper regimen, or placebo + 52-week corticosteroid taper regimen. In Period 2, patients who received upadacitinib and achieved remission for at least 24 weeks prior to end of Period 1 were re-randomised to either continue upadacitinib or switched to placebo. Although the trial included two doses of upadacitinib, the company stated that the anticipated market authorisation is for a 15 mg dose in patients with GCA. Therefore, this submission only contains efficacy data for the upadacitinib 15 mg dose. The primary analysis for all efficacy endpoints was based on the ITT population (reported in CS 2.6.1).

A total of 209 patients received upadacitinib at a dose of 15 mg and 112 received placebo in Period 1 and were included in the ITT population for the safety and efficacy analysis.

Patients were recruited to the trial from 100 sites located in 23 countries in Europe (including the UK), North America, Israel, the Russian Federation, and Asia Pacific. In response to clarification question A2, the company confirmed that 19 patients were from the UK. Demographic and baseline clinical characteristics were balanced across trial arms; approximately 70% of patients had new-onset GCA and 30% had relapsing disease. Ninety four percent of the population were white with a mean age 70.8 years and 71.6 years in the upadacitinib 15 mg and placebo treatment arms, respectively.^{60, 61} baseline patient characteristics were reported in CS Section 2.3.1.2 (Table 5; Page 58). The company stated that expert opinion from clinicians in the UK agreed that the trial demographics were reflective of a UK population. Demographic characteristics of SELECT-GCA patients were quite similar to those reported in a hospital-based, retrospective cohort study that aimed to assess the demographic variation of GCA amongst the population of Sheffield, England.⁷ Patients in the cohort were predominantly white British or Irish (94.3%) with a mean age of 72.2.

The following efficacy endpoints were evaluated in SELECT-GCA trial:

Proportion of patients achieving sustained remission at Week 52 (primary endpoint),

Proportion of patients achieving sustained complete remission from Week 12 through Week 52,

Cumulative CS exposure through Week 52,

Time to first GCA flare through Week 52,

Proportion of patients who experience at least one GCA flare through Week 52,

Rate of CS-related adverse events (AEs) through Week 52,

Change from Baseline in the 36-item Short Form Quality of Life Questionnaire at Week 52,

Change from Baseline in FACIT-Fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue) at Week 52,

Change from Baseline in EQ-5D-5L (Five Dimensions Five Levels Questionnaire) at Week 8, 24, and 52.

2.2.2 Risk of bias SELECT-GCA

Critical appraisal of SELECT-GCA was carried out using the revised Cochrane risk-of-bias tool for randomised trials (RoB2).⁴⁹ Risk of bias assessment of the trial is summarised in the CS Table 8 with full assessment provided in CS Appendix B, Table 29.

The EAG agrees with the company's judgements. Overall, SELECT-GCA was a well-designed trial with the appropriate steps taken to minimise bias where possible. The trial was deemed to be at low risk of bias across all risk of bias domains. The comparison of the company's assessment and the EAG's assessment of risk of bias in the trial using the revised Cochrane RoB2 tool can be seen in Table 7.

Table 7: Comparison of company and EAG risk of bias assessment of SELECT-GCA

Checklist questions	Company assessment	EAG assessment

1. Randomisation		
1.1 Was the allocation sequence random?	Y	Y- Randomisation was performed with the use of an interactive-response system.
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	Y- Investigators with direct oversight of the conduct and management of the trial were unaware of the trial group assignments until the last patient completed the week 52 visit.
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N	N
Risk of bias judgement	Low	Low
2. Deviations from intended interventions		
2.1 Were participants aware of their assigned intervention during the trial?	N	N
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	N
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Y
Risk of bias judgement	Low	Low
3. Missing outcome data		
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Y- intention to treat analysis for all randomised participants who received at least 1 dose of study drug in period 1
Risk of bias judgement	Low	Low
4. Measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	N	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N	N

Risk of bias judgement	Low	Low
5. Selection of the reported result		
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Y
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	N
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N	N
Risk of bias judgement	Low	Low
Overall bias	Low	Low

2.2.3 Efficacy results SELECT-GCA

Upadacitinib at a dose of 15 mg once daily with a 26-week corticosteroid taper (n=209) showed superiority over placebo with a 52-week corticosteroid taper (n=112) with respect to sustained remission at week 52 (46.4% [95% confidence interval {CI}, 39.6 to 53.2] vs. 29.0% [95% CI, 20.6 to 37.5]; P=0.002).

The secondary endpoint of sustained complete remission at week 52 was observed in a significantly higher percentage of patients who received upadacitinib at a dose of 15 mg with a 26-week glucocorticoid taper (37.1% [95% CI: 30.5, 43.7]) than in those who received placebo (16.1% [95% CI: 9.3, 22.9]).

The median cumulative exposure to corticosteroid over the course of 52 weeks was significantly lower with upadacitinib 15 mg (1,615 mg [95% CI: 1,615, 1,635]) compared with the placebo arm (2,882 mg [95% CI: 2,762, 3,253]) (p < 0.0001).

Treatment with upadacitinib 15 mg resulted in a lower risk of GCA flare through week 52 than placebo, and significantly fewer patients in the 15-mg upadacitinib group had at least one GCA flare (34.3% [95% CI: 27.4, 42.4]) compared with the placebo arm

(55.6% [95% CI: 42.9, 69.2]) ($p = 0.0014$). Additionally, there was a significant increase in the time to first GCA flare through Week 52 was in the upadacitinib 15 mg arm compared with the placebo (hazard ratio 0.57 [95% CI: 0.399, 0.826]) ($p = 0.0025$).

Treatment with upadacitinib at a dose of 15 mg led to a significant reduction from baseline in fatigue and improvement from baseline in quality of life through week 52 than placebo. Summary of secondary endpoint results is shown in CS, Table 10, page 68.

2.2.4 Safety SELECT-GCA

Safety outcomes over the course of 52 weeks were generally similar in the upadacitinib and placebo groups. The percentage of patients who experienced any treatment emergent adverse events (TEAEs) or serious adverse events (SAEs) were generally similar between upadacitinib 15 mg arm (96.7% and 23.0%, respectively) and the placebo arm (94.6% and 21.4%, respectively). The incidence of TEAEs leading to discontinuation of upadacitinib or placebo was lower with upadacitinib (17.2%) than with placebo (25.9%).

Common adverse events that emerged during treatment in the patients receiving upadacitinib 15 mg included headache (16.3%), arthralgia (13.9%), hypertension (13.4%), and coronavirus disease 2019 (Covid-19; 13.4%).

According to Common Terminology Criteria for Adverse Events (CTCAE), adverse events that emerged during treatment were predominantly mild to moderate ($\leq$ Grade 2) in both treatment arms (65.5 – 67.0%). TEAEs $\geq$ Grade 3 (severe to death) were comparable between upadacitinib 15 mg (31.1%) and placebo arms (27.7%).

Four deaths occurred during the period after initiation of upadacitinib or placebo through 30 days after the last dose was received: two in the 15-mg upadacitinib group and two in the placebo group. One death in the 15-mg upadacitinib group was linked to Covid-19 and the other was adjudicated as an unexplained cause. One death in the placebo arm was attributed to sepsis and the other adjudicated to be caused by acute pancreatitis.

Importantly, no significant difference in corticosteroid related AEs were observed between the trial arms, even for those with relatively common occurrence. Indeed, a higher proportion of patients in the upadacitinib arm (■) experienced TEAEs with

reasonable possibility of being related to prednisone/prednisolone (or matching placebo) as assessed by the investigator, compared with ■ of participants in the placebo arm (CS Document B, Table 11).

2.2.5 Subgroup analysis

SELECT-GCA included prespecified subgroup analyses of the primary outcome. These included age, sex, race, prior use of IL-6 inhibitors, baseline corticosteroid dose at baseline, newly diagnosed or relapsing GCA and history of unequivocal symptoms of polymyalgia rheumatica (PMR) without cranial symptoms of GCA. A number of subgroups specified on the NICE final scope were not addressed in the trial. These include:

Patients who have experienced previous corticosteroid toxicity or have pre-existing conditions likely to be exacerbated by corticosteroids. The company stated that clinicians did not deem this as a clinically distinct subgroup and that these patients will still receive corticosteroids in clinical practice to control disease relapse given the lack of alternative treatment options.

Patients who have had up to 12 months of tocilizumab & patients unsuitable to tocilizumab. The company stated that patients who are unsuitable for tocilizumab, or following tocilizumab completion would also receive corticosteroids in clinical practice.

Across nearly all evaluated subgroups, including age, sex, new-onset or relapsing GCA, and baseline corticosteroid dose, efficacy of upadacitinib 15 mg was generally consistent with that observed in the overall trial population (Figure 9, CS, page 73).

Subgroups relevant to the NICE scope included patients with new onset and relapsing GCA. The analysis showed that with either new onset or relapsing GCA, a significantly higher percentage of patients achieved sustained remission at Week 52 in the upadacitinib 15 mg arm compared with the placebo arm (new onset GCA: 48.1% versus 32.2%; relapsing GCA: 42.3% versus 22.2%).

In new onset and relapsing GCA subgroups, sustained complete remission from Week 12 through Week 52 was achieved in a significantly higher percentage of

patients in the upadacitinib 15 mg arm compared with the placebo arm (new onset: ■■■ versus ■■■ relapsing GCA: ■■■ versus ■■■).

The median cumulative corticosteroid exposure was significantly lower in the upadacitinib 15 mg arm compared with the placebo arm for both new onset (■■■ mg versus ■■■ mg) and relapsing GCA (■■■ mg versus ■■■ mg) subgroups.

The number of patients who experienced at least 1 GCA flare through Week 52 was significantly lower in the upadacitinib 15 mg arm compared with the placebo arm for both new onset (■■■ versus ■■■ and relapsing GCA (■■■ versus ■■■) subgroups. Summary of secondary endpoint results by new onset and relapsing GCA subgroup is shown in CS Table 54, Appendix C.

2.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company did not conduct any indirect comparison or multiple treatment comparisons in its main submission. The EAG considered the lack of indirect comparison with tocilizumab for patients with relapsing GCA as a major omission in the CS, and requested the company to provide such data in one of the EAG's clarification questions (A1). Nevertheless, the company re-iterated their justifications for excluding tocilizumab, which the EAG disagrees with (as described earlier in Section 1.3) and did not provide any comparative evidence against a comparator other than placebo.

2.4 Critique of the indirect comparison and/or multiple treatment comparison

As described above, no comparative evidence was put forward by the company despite that the EAG requested the company to provide an indirect comparison between upadacitinib and tocilizumab for patients with relapsing GCA as the latter was a treatment recommended by NICE in TA518.

2.5 Additional work on clinical effectiveness undertaken by the EAG

Given the crucial influence disease relapsing/flare has on cost-effectiveness analyses, the EAG has closely examined time to event data provided in the clinical effectiveness section, and cross-examined the company's curve fitting based on these data to inform cost-effectiveness assessments. These are described in section 2.5.1 below. In addition, given the critical omission of evidence on comparative effectiveness between upadacitinib and tocilizumab, the EAG collated evidence from respective pivotal trial for upadacitinib (SELECT-GCA) and tocilizumab (GiACTA) for the treatment of GCA, and conducted adjusted indirect comparisons between the two treatments. Findings are provided in section 2.5.2.

2.5.1 EAG's exploration of the company's time to event (flare) analyses

2.5.1.1 Time to event data submitted by the company

The submission compared upadacitinib + 26-week corticosteroid tapering versus placebo + 52-week corticosteroid tapering. The observed data in the submission extended to 52 weeks. The base case life-time economic model required extensive extrapolation beyond observed data. The patient numbers entering 52 weeks observation were modest (112 and 209 for the control and intervention arms respectively). As such the EAG considers the data base relatively weak. The company relied heavily on clinical advice to establish "valid" modelling.

The company's submission contained Kaplan-Meier (K-M) analyses of time to first flare (TTFF). Parametric models of K-M analysis were developed for each arm and lognormal selected as best option. The first two years of lognormal model for the upadacitinib arm was employed for economic modelling; after two years the upadacitinib lognormal model was adjusted for waning of effectiveness using lognormal data from the placebo arm. As such the placebo arm TTFF defines the control arm but also strongly influences most (38 of 40 years) of the model for the intervention arm. As such the selection of placebo arm data and modelling has substantial impact on the company's economic model.

Importantly, in response to clarification B1, the company informed the EAG that the K-M plots for TTFF were incorrect (digitised rather than IPD) and supplied new corrected K-M data for subgroups and the ITT population. This necessitated EAG rewriting their critique at a late stage.

2.5.1.2 ITT population Kaplan-Meier analyses presented by the company in clarification

In response to clarification A15, the company presented the corrected ITT TTFF K-M plot for both arms and provided the underlying data (clarification Table 13). The corrected plot is somewhat more pessimistic for PBO than that was first submitted. The company's new plot ([Figure 1](#)) and EAG plot (Figure 2) are shown below. A difference in the EAG plot from the company clarification figure is the start numbers at risk; this may be due to some patients being coded at zero days and were lost from the analysis. All other risk table data is the same as the company. The new ITT K-M for PBO is more pessimistic than the original submission (Figure 3).

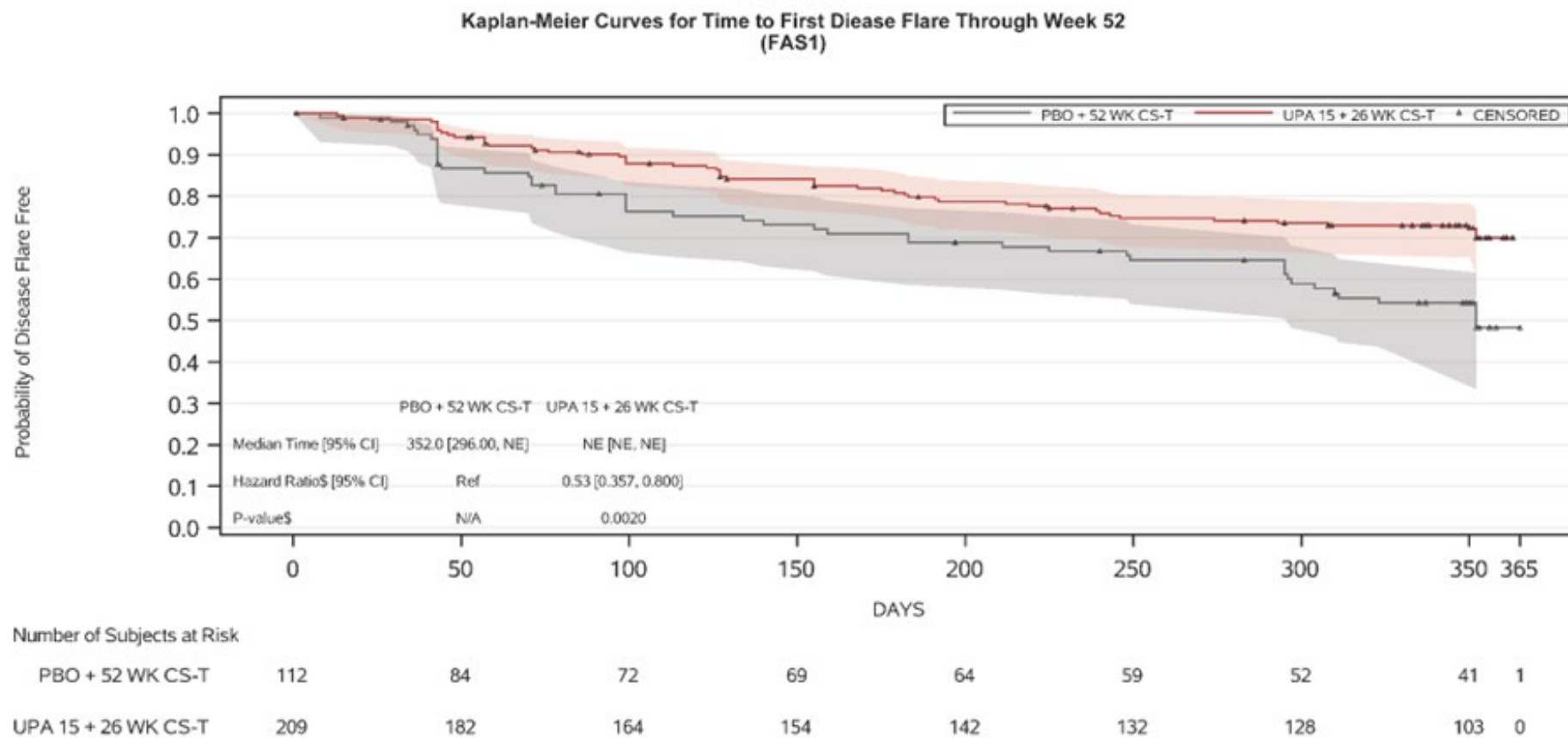


Figure 1: Company's Corrected K-M plots for ITT PBO and Upadacitinib TTFF
(Reproduced from Company clarification Figure 4)

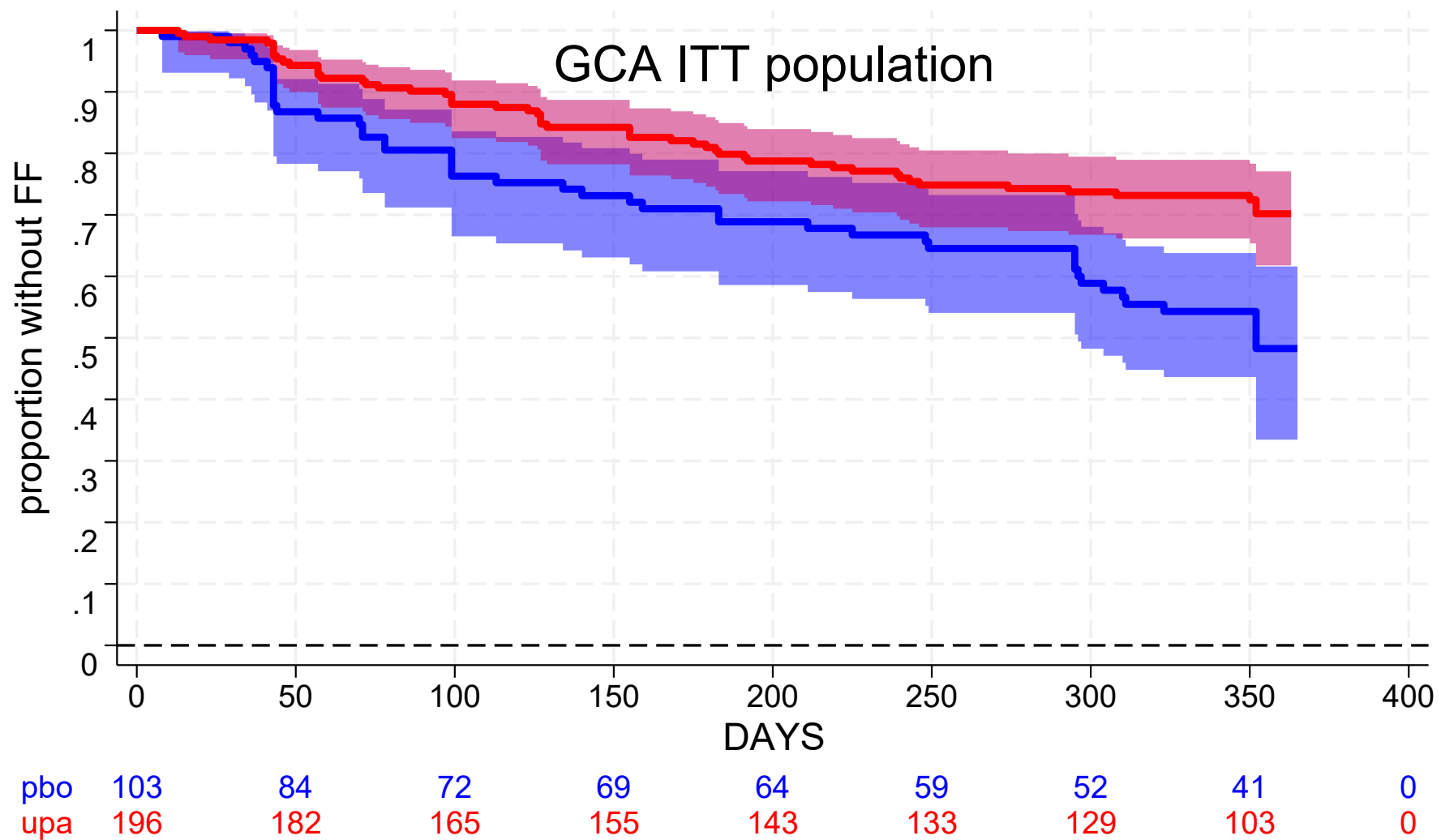


Figure 2: EAG KM plots based on data supplied in clarification.

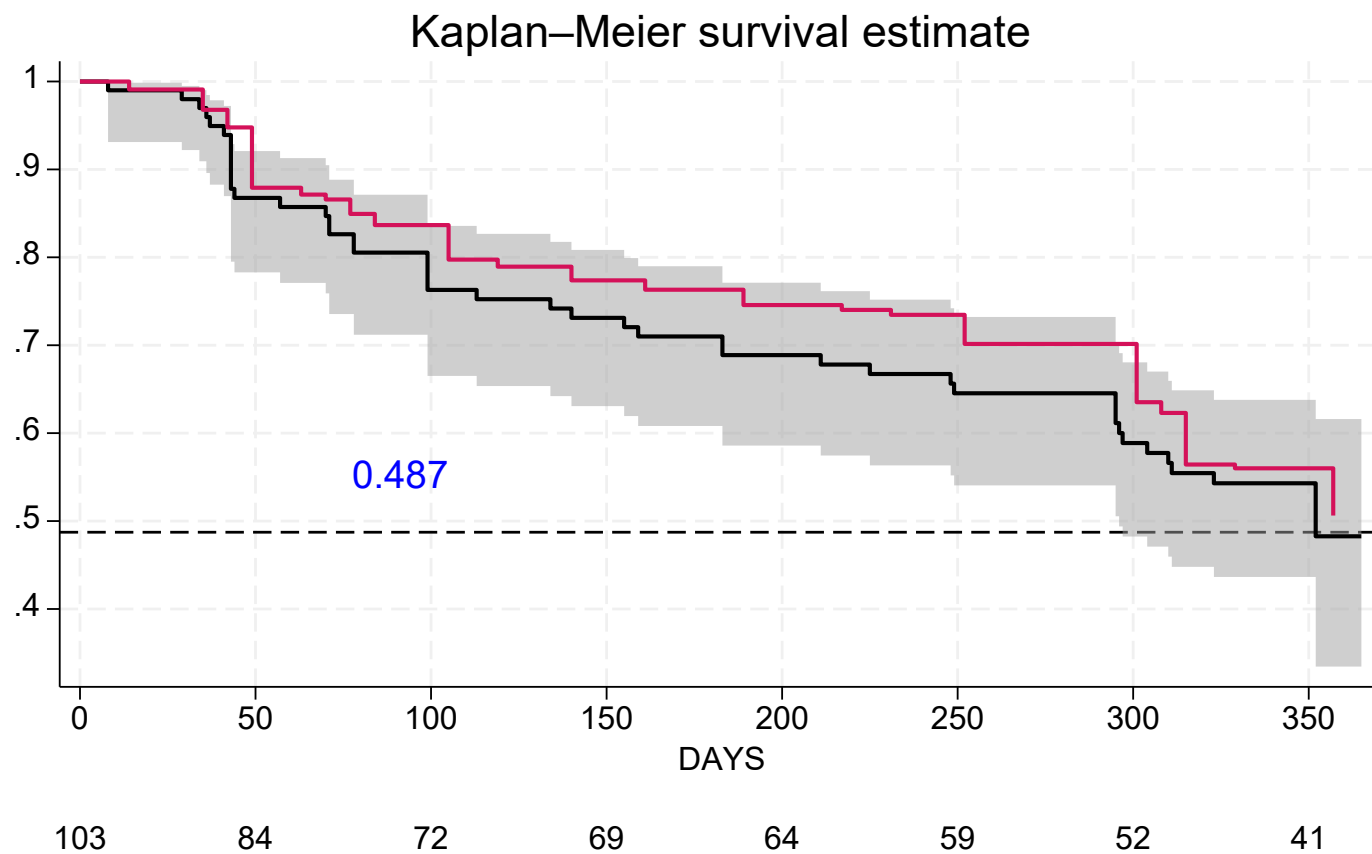


Figure 3: Company's Corrected K-M plot for ITT PBO TTFF compared to that originally submitted K-M (red line)

The K-M plot for the PBO TTFF exhibits multiple changes in trajectory (Figure 4). This suggests presence of two or more subgroups with distinctly different TTFF properties and renders it unlikely that parametric models with limited flexibility will provide good fit to the PBO data.

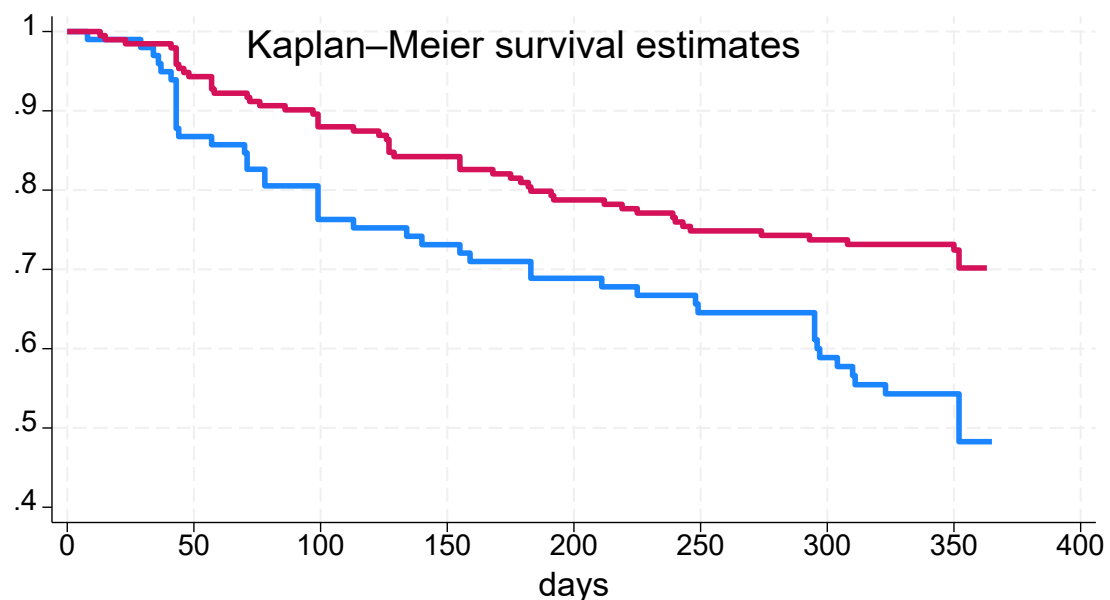


Figure 4: Changing trajectory in the PBO K-M plot (blue line)

A PBO arm smoothed hazard plot (Figure 5) suggests that for much of the observed TTFF the hazard first decreases and then increases, consistent with trajectory changes in the K-M.

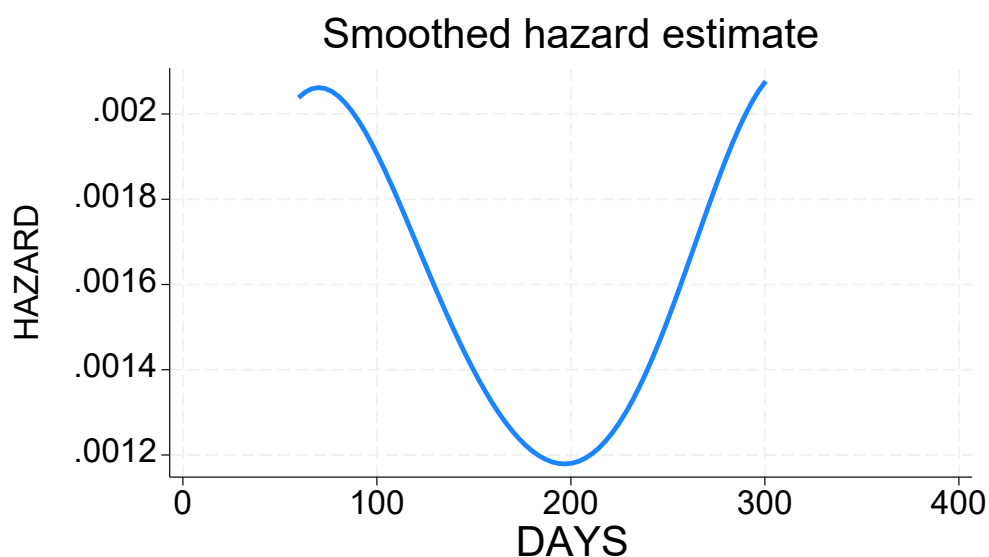


Figure 5: Smoothed hazard plot for corrected ITT PBO TTFF

Parametric modelling ITT population

The company employed seven parametric models to model both arms and selected lognormal models as the best candidate for extrapolation. This choice was based on AIC values for models and on conformity to expert clinical advice on predicted extrapolation beyond the observed 52 months.

AIC scores for EAG models fit to KM data are summarised in Table 8 ranked according to AIC values and intervention. Lognormal and ggamma models rank best across both arms, however differences in AIC scores between models are trivial for both arms and fail to offer clear indication for best candidate model.

Table 8: Akaike Information Criteria scores for parametric models of corrected K-M

Arm	N	Model	AIC	df
upadacitinib	196	ggamma	336.9065	3
upadacitinib	196	lognormal	338.3652	2
upadacitinib	196	Gompertz	341.1318	2
upadacitinib	196	exponential	342.0055	1
upadacitinib	196	loglogistic	342.1231	2
upadacitinib	196	Chen	342.6764	3
upadacitinib	196	Weibull	343.8443	2
upadacitinib	196	Rayleigh	344.0055	2
upadacitinib	196	bathtub	349.891	2
PBO	103	lognormal	234.6862	2
PBO	103	ggamma	235.8864	3
PBO	103	exponential	236.199	1
PBO	103	loglogistic	237.0818	2
PBO	103	Gompertz	237.8071	2
PBO	103	Weibull	238.1856	2
PBO	103	Rayleigh	238.199	2
PBO	103	bathtub	239.4595	3
PBO	103	Chen	242.3617	2

All ITT PBO parametric models including lognormal and generalised gamma present similar but very poor fit to the PBO KM arm data (Figure 6 and Figure 7). Similarly for the ITT Upadacitinib group all models are similar over the observed KM period but none present a good visual fit (Figure 8).

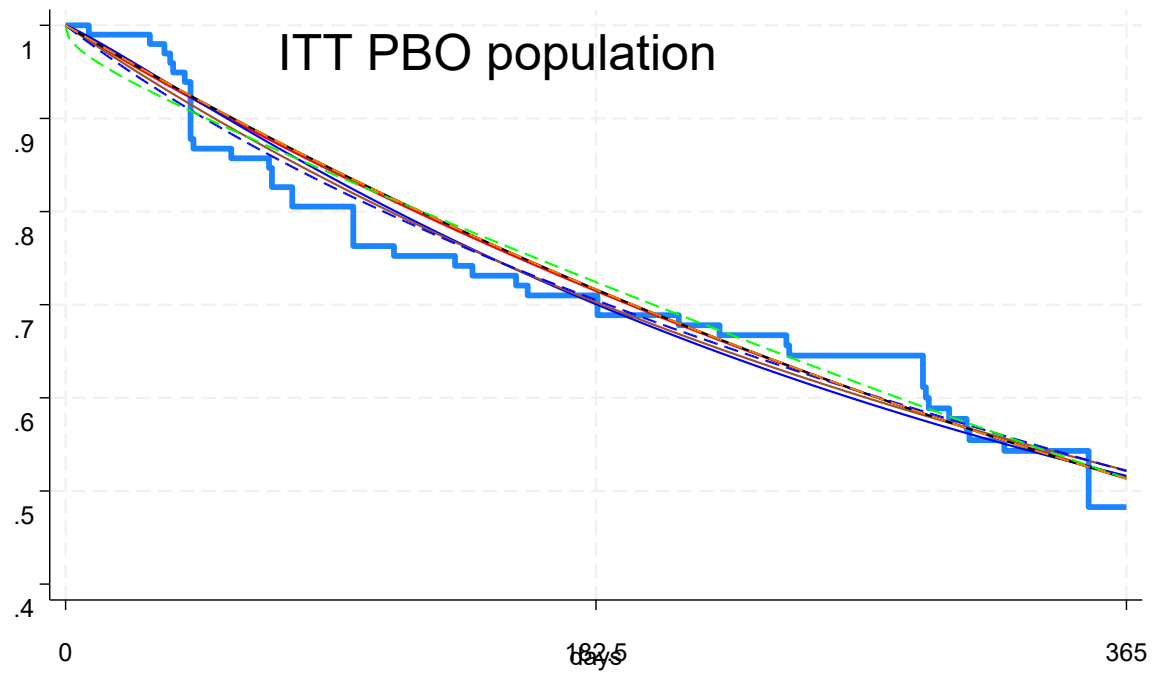


Figure 6: Parametric models for ITT PBO population (Weibull, loglogistic, Gompertz, exponential, bathtub, Chen and Rayleigh models over observed data range)

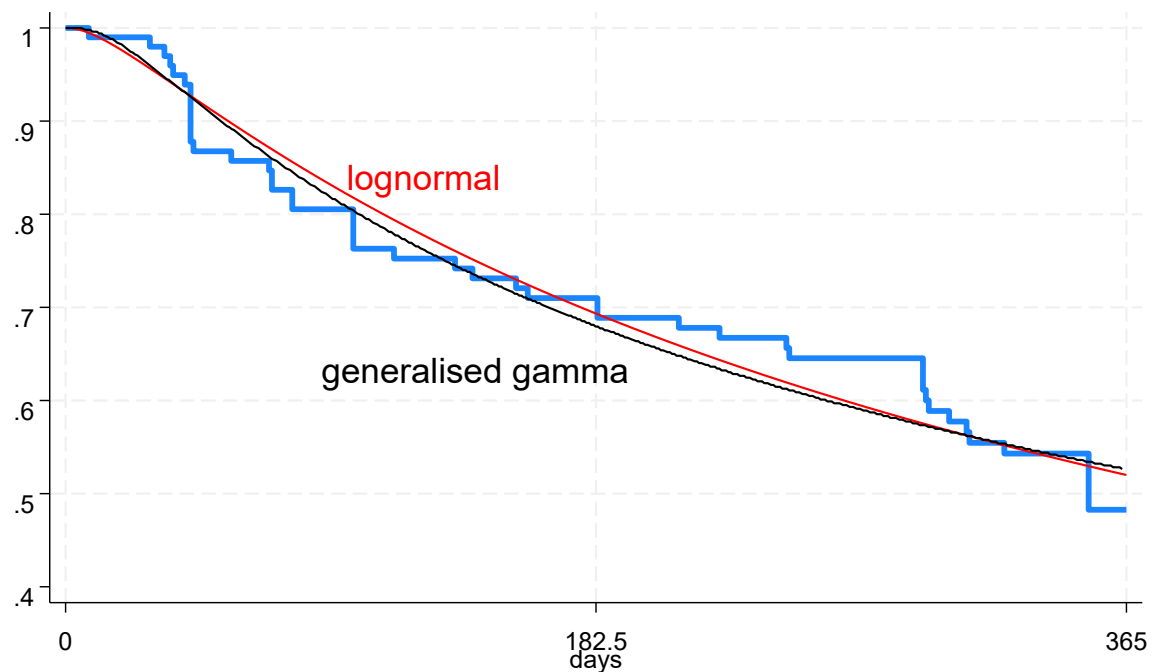


Figure 7: Lognormal and generalised gamma models for ITT PBO.

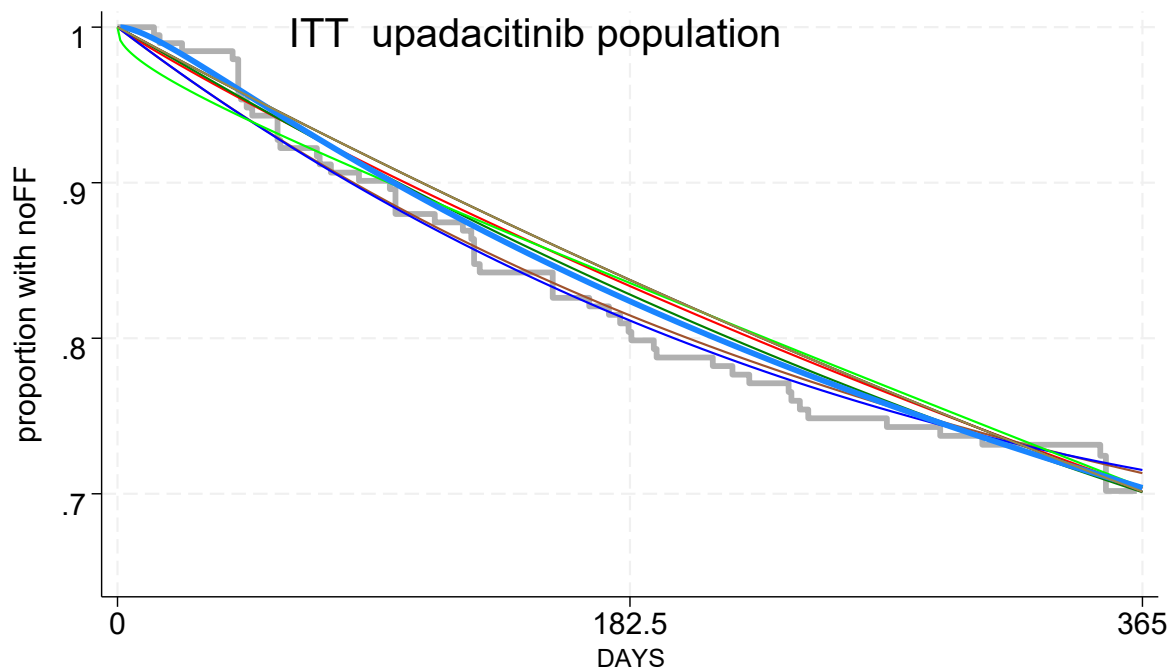


Figure 8: Parametric models for ITT upadacitinib population Weibull, loglogistic, Gompertz, exponential, bathtub, Chen, lognormal and Rayleigh models over observed data range (the lognormal model is indicated by the thick blue line)

On extrapolation beyond the observed data to the lifetime horizon the models generate a wide range of predicted TTFF for both PBO and Upadacitinib arms (Figure 9 and Figure 10). In view of the trivial difference between models for both AIC scores and similar but poor fit across the observed KM data these results mean that the company's strategy for TTFF depends almost exclusively on clinical advice. In EAG opinion the resulting selection could be tested using available external evidence.

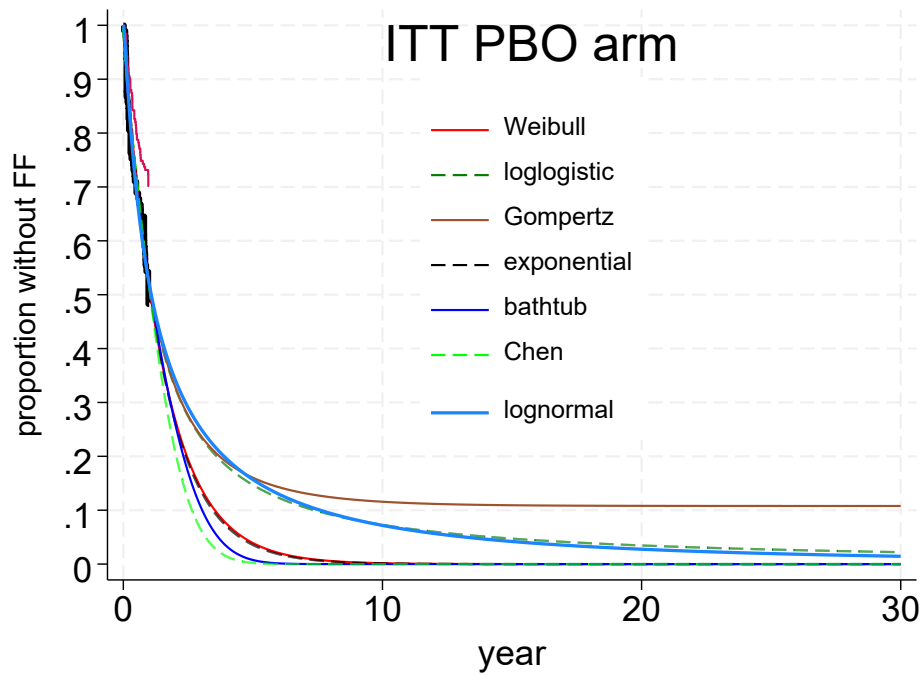


Figure 9: Parametric models extrapolated to 30 years (PBO)

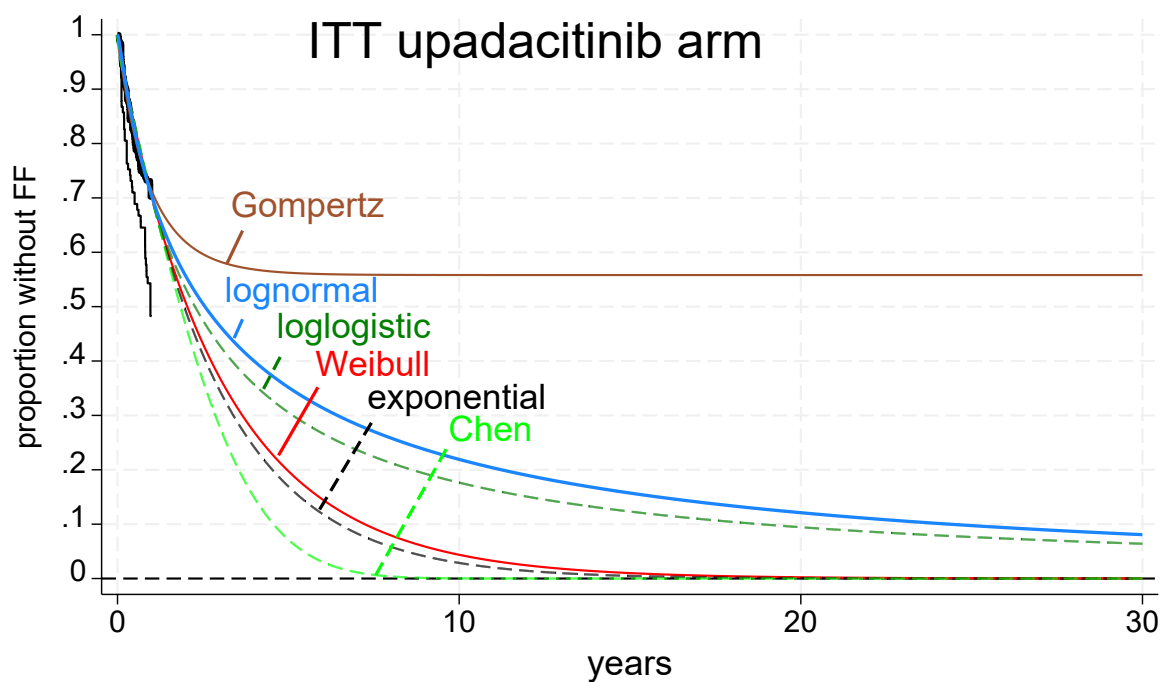


Figure 10: Parametric models extrapolated to 30 years (Upadacitinib)

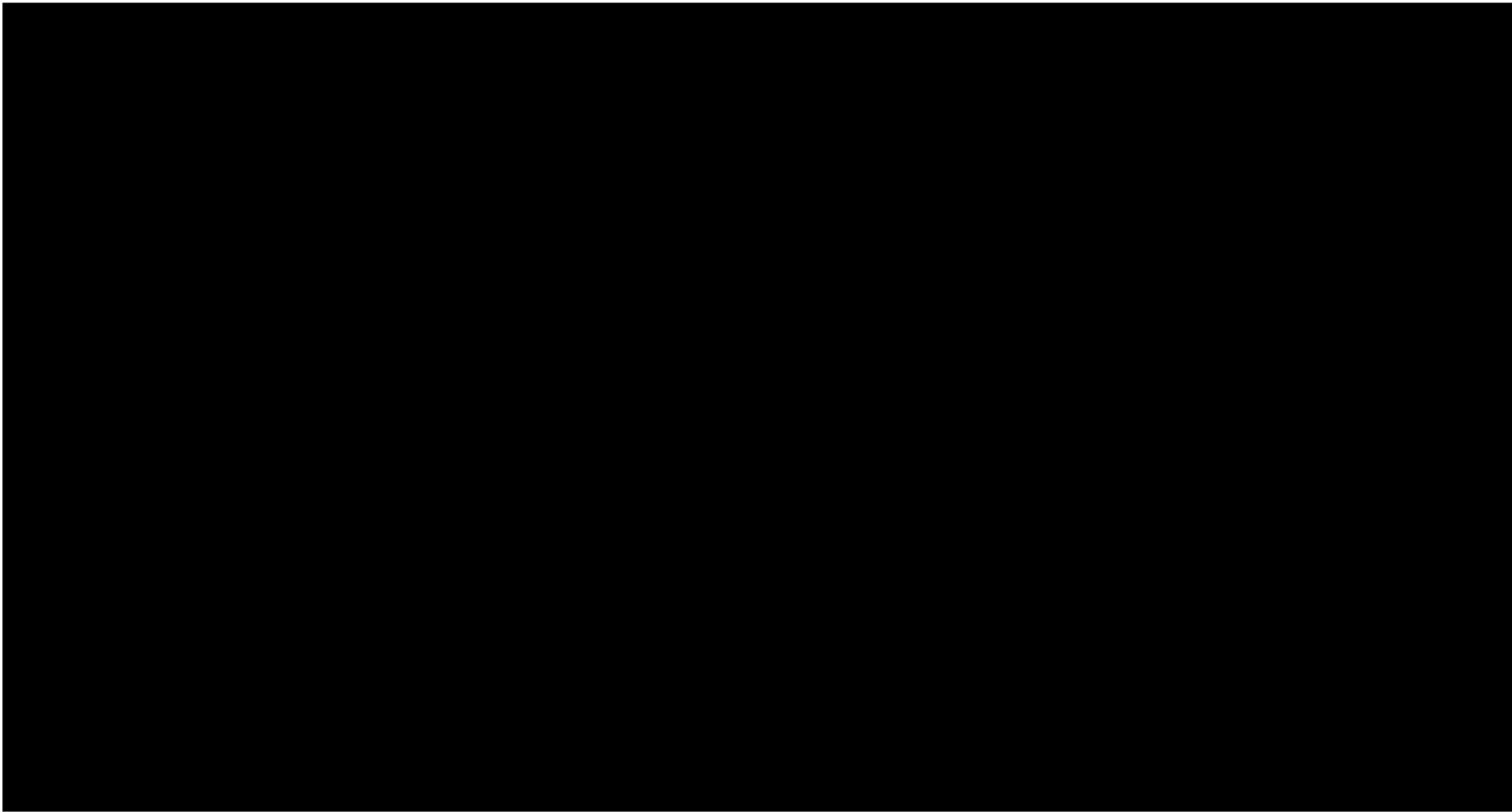
2.5.1.3 New onset subgroup

The company's corrected K-M plots for placebo and upadacitinib in the newly-diagnosed subgroup is shown in [REDACTED], and the EAG reconstructed K-M plots based on updated dataset provided by the company is shown in [REDACTED]. A difference from the company's clarification figure is the start numbers at risk; this may be due to some patients being coded at zero days and were lost from the analysis. All other risk table data is the same as the company.

The KM plot 95% CIs overlap somewhat between arms ([REDACTED]). AIC scores for specified parametric models of the PBO and upadacitinib KM for new-onset subgroups (fit separately to each arm) are summarized in Table 9, ranked according to AIC value.

Table 9: AIC scores for parametric models of new onset subgroup

	N	Model	AIC	df
upadac	140	ggamma	238.296	3
upadac	140	lognormal	240.048	2
upadac	140	Gompertz	240.682	2
upadac	140	bathtub	242.467	3
upadac	140	loglogistic	242.936	2
upadac	140	exponential	243.126	1
upadac	140	Weibull	244.119	2
upadac	140	Rayleigh	245.126	2
upadac	140	Chen	248.152	2
	N	Model	AIC	df
PBO	70	lognormal	161.605	2
PBO	70	ggamma	161.986	3
PBO	70	Gompertz	163.367	2
PBO	70	loglogistic	163.657	2
PBO	70	exponential	163.778	1
PBO	70	Weibull	165.269	2
PBO	70	bathtub	165.405	3
PBO	70	Rayleigh	165.778	2
PBO	70	Chen	168.846	2



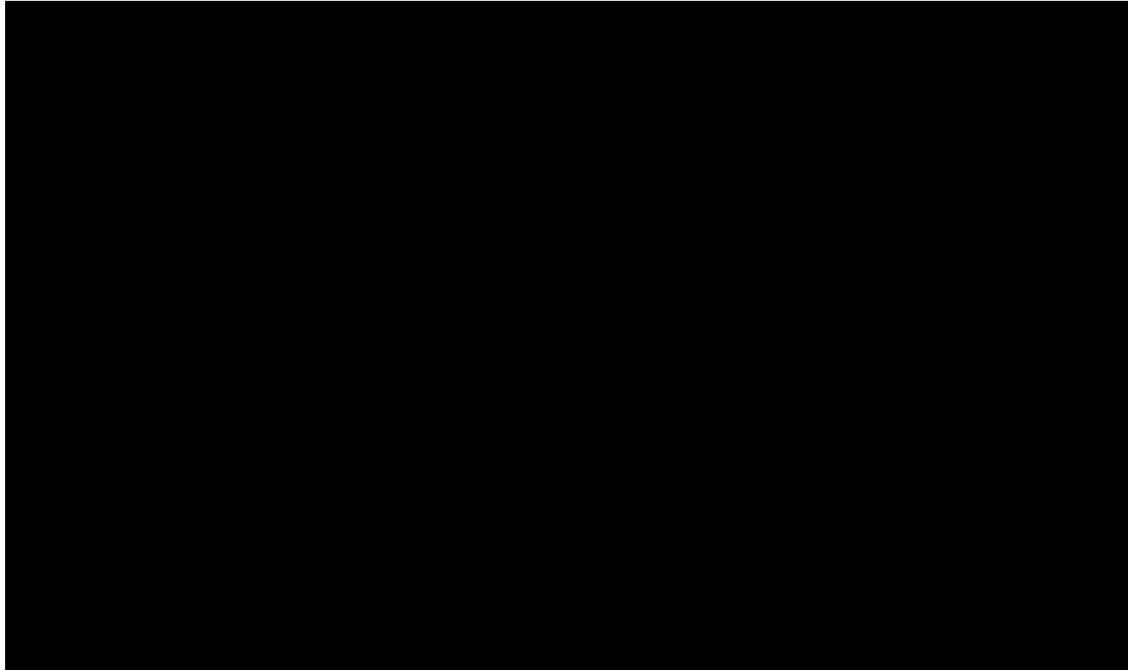
11 [Redacted text]

[Redacted text]



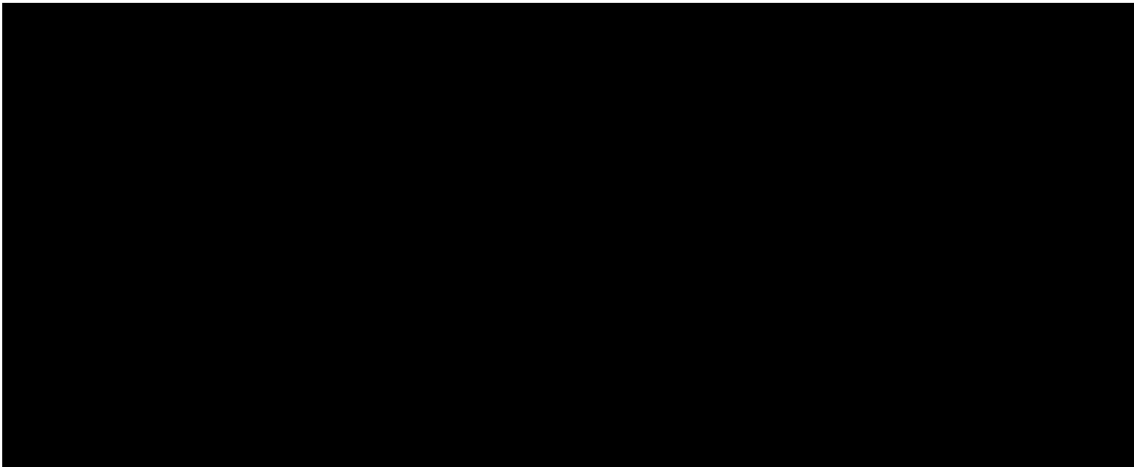
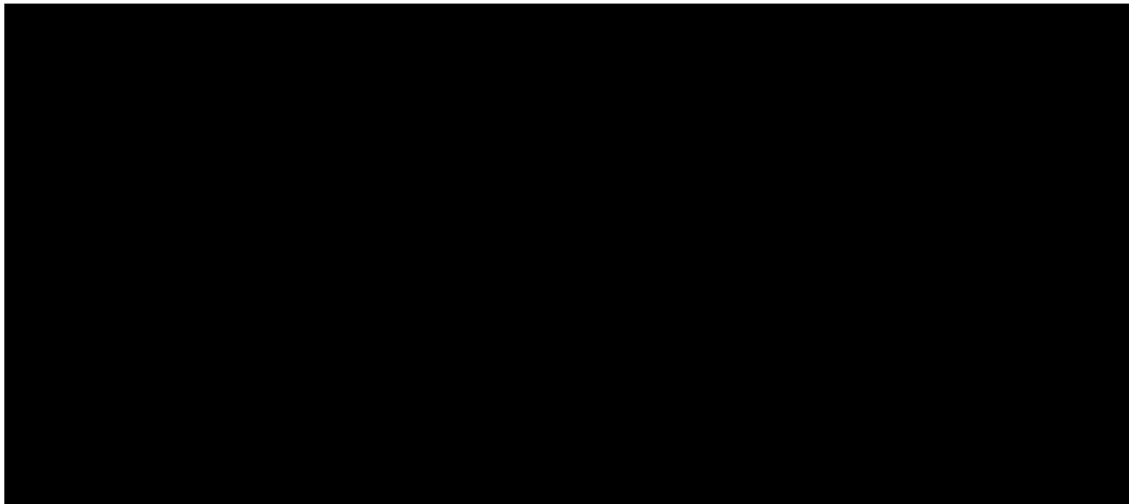
12

Differences in AIC scores between most models are trivial making it difficult to select a most appropriate candidate model common for both arms. The models most favoured by the company were Gompertz and lognormal (██████████) justified on basis of clinical advisors' opinion regarding likely extrapolation beyond the one year of observed data.



13

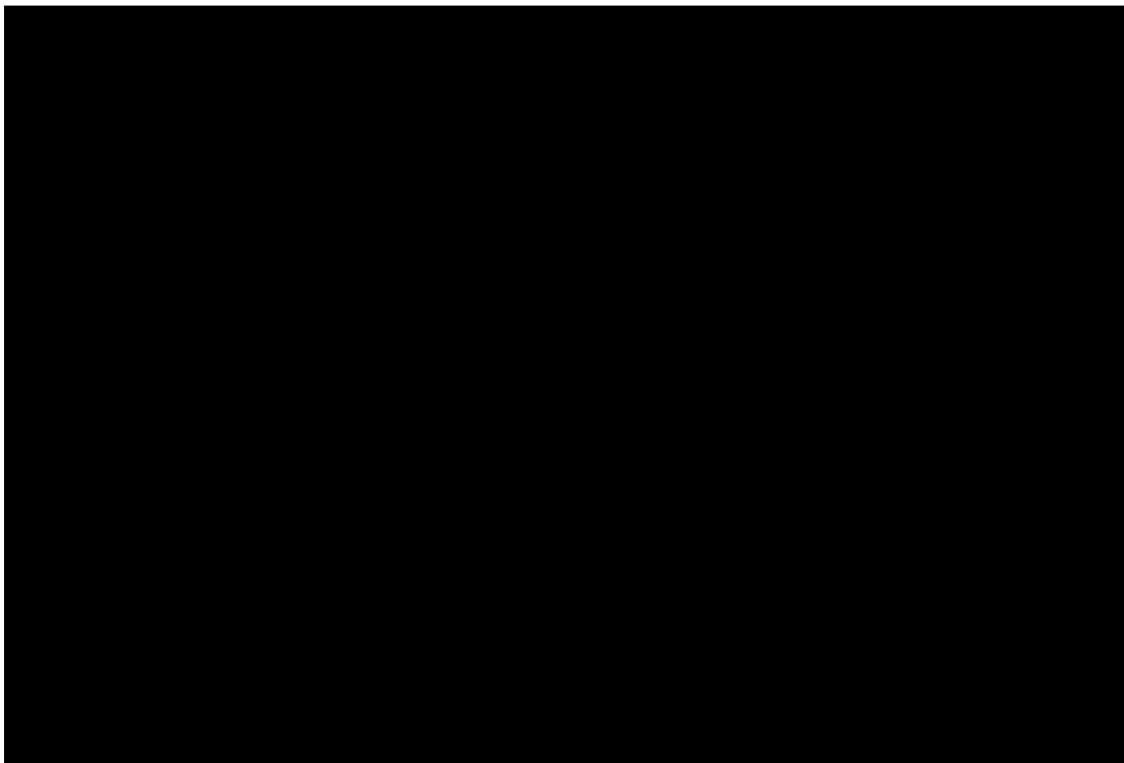
The Gompertz model (fit separately to each arm) predicts that the effectiveness of PBO and of upadacitinib in preventing FF never wanes from approximately five years into the future of a whole life-time. In contrast the lognormal model allows a continuous waning of effectiveness. At 3 years lognormal model predicts █████ in the PBO arm have not experienced FF; this coincides closely to that seen in the KM for the new onset subgroup reported from the GiACTA trial.⁶² In the GiACTA trial at three years the KM analysis suggests ~42% of the new-onset tocilizumab subgroup had not experienced FF this compares with █████ for upadacitinib new-onset group lognormal model. Generalised gamma models offer intermediate extrapolations between Gompertz and lognormal for both arms (██████████).



The difference between Gompertz generalised gamma and lognormal models is sufficiently substantial to suggest a need for comparison with further external evidence.

In summary the short follow up and small number of participants in the new-onset subgroup represent limitations that make it difficult to decide which, or if any, of the available models can be used with confidence in determining long term outcome for TTFF.

Weibull, exponential, Chen and Rayleigh models are shown in [REDACTED] these alternatives offer various degrees of waning of effectiveness more pessimistic than the lognormal, Gompertz, and generalised gamma models.



15

2.5.1.4 Relapsed subgroup

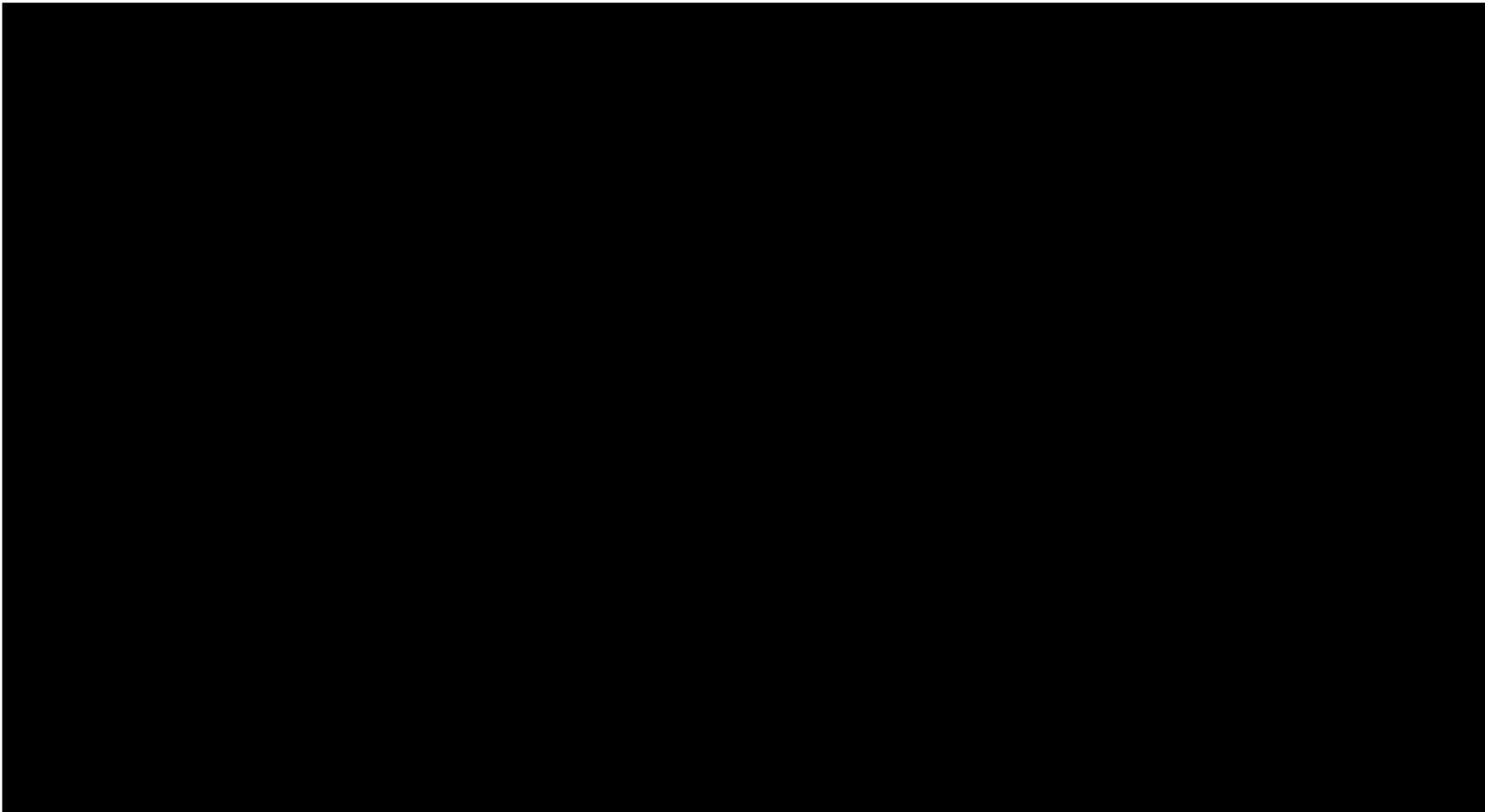
The company corrected K-M plots for placebo and upadacitinib in relapsed subgroup is shown in [REDACTED], and the EAG reconstructed K-M plots based on updated dataset provided by the company is shown in [REDACTED]. A difference from the company's clarification figure is the start numbers at risk; this may be due to some patients being coded at zero days and were lost from the analysis. All other risk table data is the same as the company.

Small numbers of patients in the PBO arm result in wide 95% CIs ([REDACTED] and Figure 17). KM trajectories change several times over 1 year and the plots for PBO and upadacitinib arms cross over. In the GiACTA trial by contrast relapsing PBO and tocilizumab arms have consistent trajectories over 3 years and do not cross over (Figure A in Stone 2022 ⁶²). AIC scores for specified parametric models of the PBO and upadacitinib KM for relapsing subgroup (fit separately to each arm) are summarized in Table 10, ranked according to AIC value.

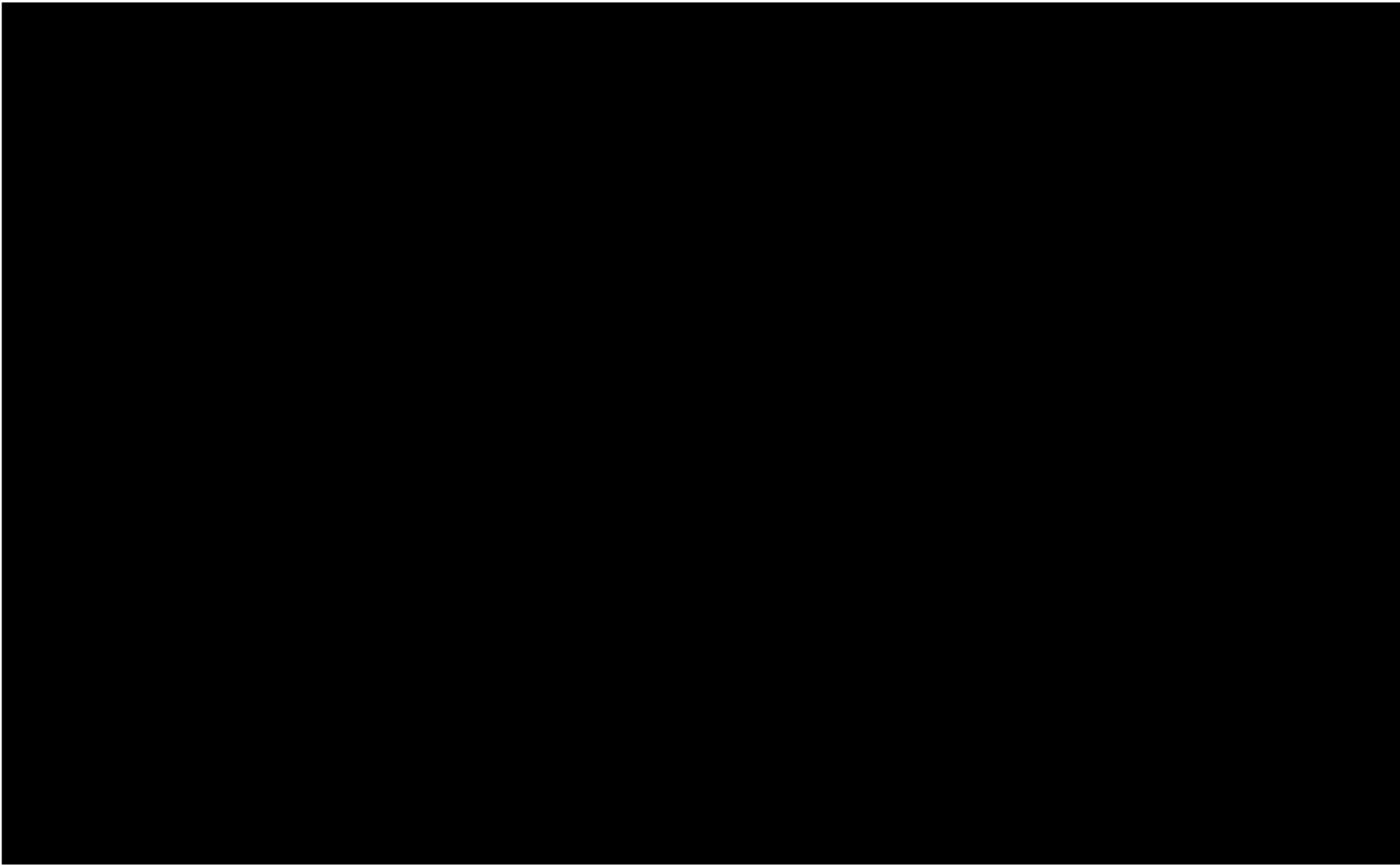
Table 10: AIC scores for parametric models of relapsing subgroup

	N	Model	AIC	df
PBO	33	exponential	74.3761	1
PBO	33	Gompertz	75.1723	2

PBO	33	Rayleigh	75.4601	2
PBO	33	Weibull	75.4907	2
PBO	33	lognormal	75.7387	2
PBO	33	Chen	75.8903	2
PBO	33	loglogistic	76.0322	2
PBO	33	ggamma	76.9648	3
PBO	33	bathtub	77.2595	3
upadac	55	lognormal	98.2289	2
upadac	55	ggamma	98.6875	3
upadac	55	exponential	99.1605	1
upadac	55	loglogistic	99.5426	2
upadac	55	Weibull	100.307	2
upadac	55	Rayleigh	101.141	2
upadac	55	Gompertz	101.148	2
upadac	55	Chen	102.548	2
upadac	55	bathtub	103.141	3



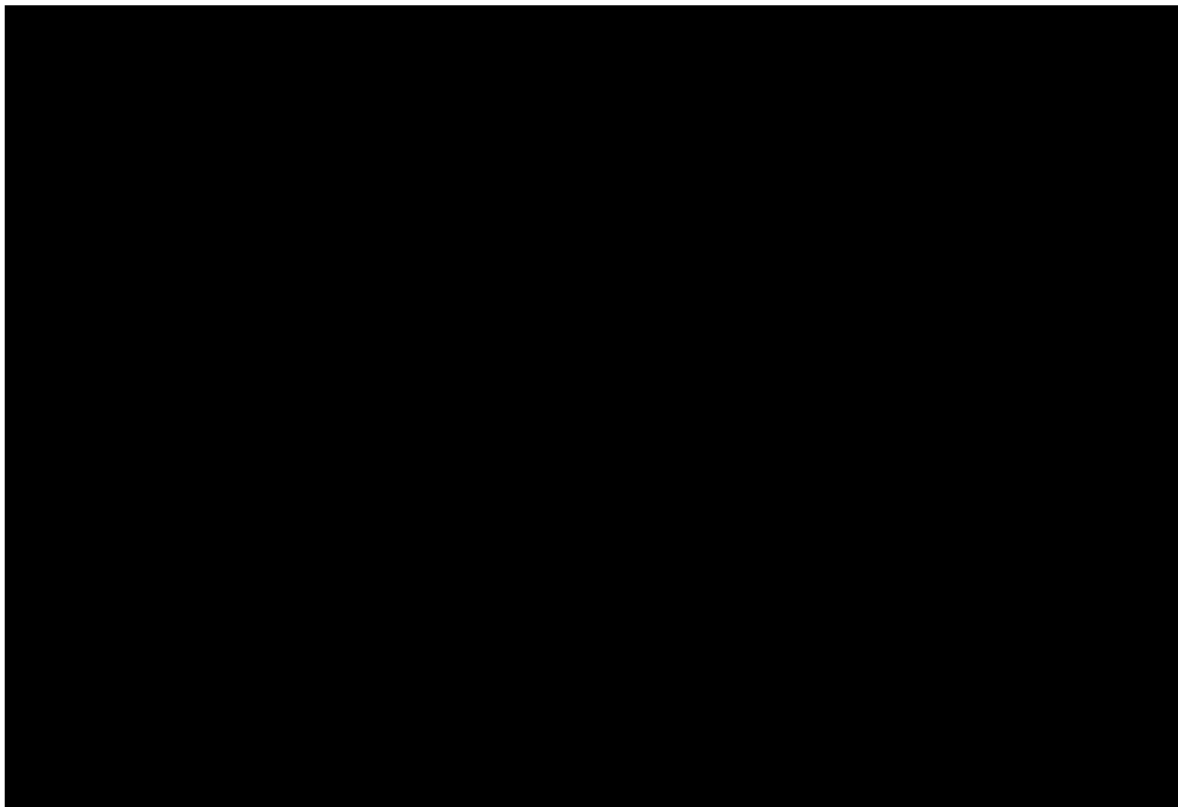
(Reproduced from company clarification response Figure 6)

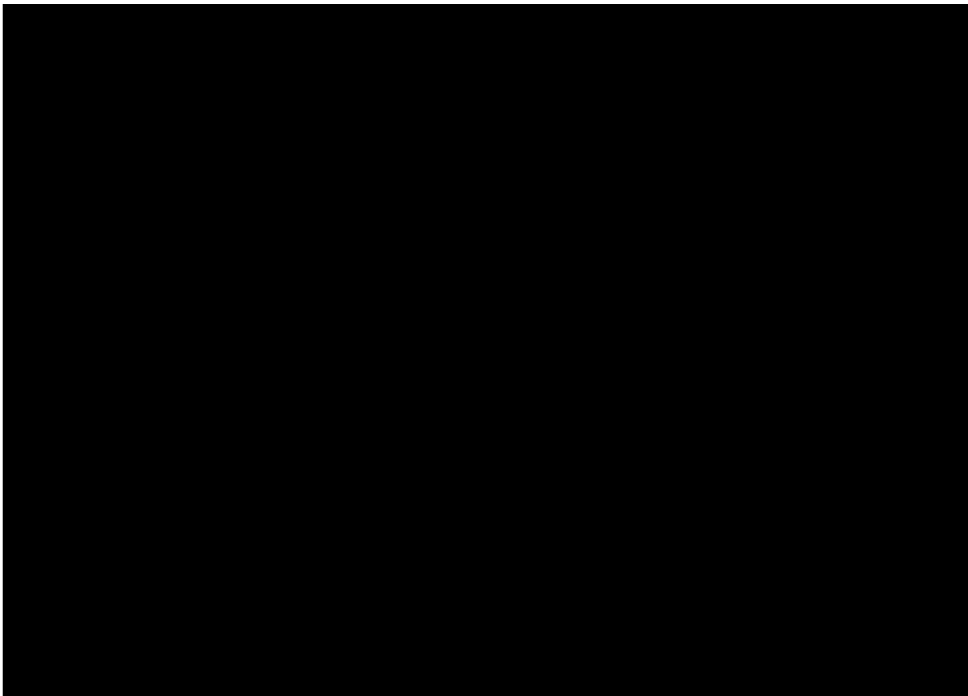


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AIC differences between models for each arm are mostly trivial and selecting a most appropriate or suitable candidate model for both arms is not possible based on AIC values. Extrapolation of specified models beyond one-year appears influenced by the number of parameters for the model, so that more flexible three-parameter models, bathtub and ggamma, generate a very pessimistic PBO while ggamma generates an extremely optimistic upadacitinib (██████). Differences between arms for exponential (constant hazard) and two parameter models (limited flexibility) predict seemingly more consistent differences between arms through time (██████
██████

In summary the EAG do not think the relapsing subgroup KM IPD is suitable for modelling.





[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.5.1.5 Technology assessment TA518 tocilizumab versus placebo

The EAG reconstructed IPD and K-M for relapsing and new onset PBO subgroups reported by Stone et al., 2022 in which 26- and 52- week tapering PBO groups and the tocilizumab dose regimens (QW and 2QW) were each pooled. Figure 23 shows results for the relapsing subgroup (N=55). After 72.9 weeks 24.5% of relapsing subgroup remain without an FF event for a further 83.6 weeks. At one year approximately 30% remain without FF. The AbbVie PBO relapsing subgroup K-M at approximately 1 year indicates just over 50% without FF; maintenance of this proportion beyond one year is unknown and can only be modelled using poor visual fit parametric models guided by clinical opinion.

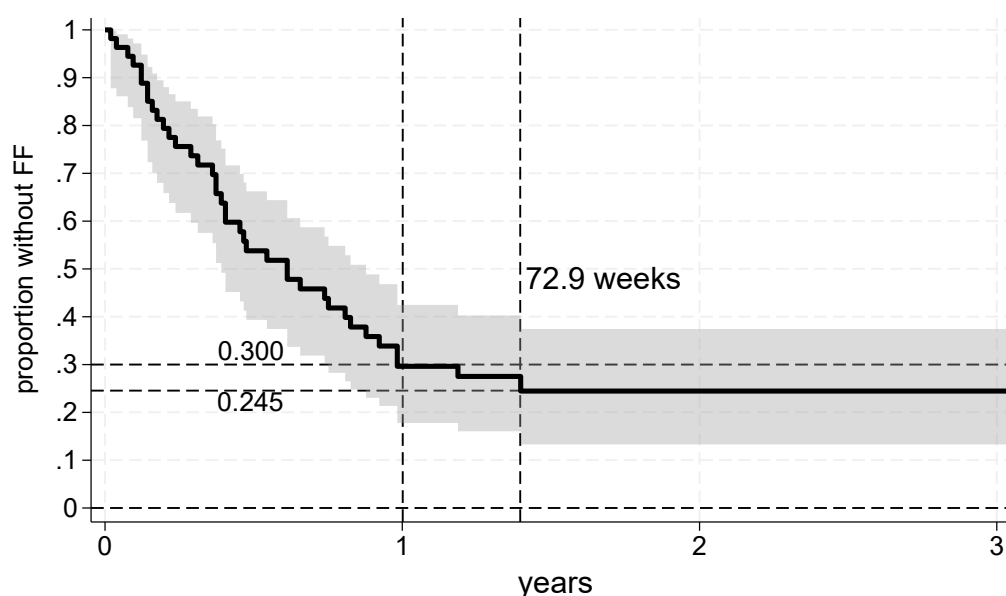


Figure 17: Reconstructed PBO K-M for the relapsing subgroup of GiACTA followed for 3 years

Figure 24 shows PBO TTFF results for the new onset subgroup (N=46). After 90.3 weeks 27.1% of new onset subgroup remain without an FF event for a further 66.3 weeks. At one year approximately 35.9% remain without FF. The AbbVie PBO new onset subgroup K-M at approximately 1 year indicates just over 50% without FF; maintenance of this proportion beyond one year is unknown and can only be modelled using poor visual fit parametric models guided by clinical opinion.

██████ shows PBO TTFF for the new-onset subgroup; from about 1.7 to 3 about 24% remain FF-free. The AbbVie PBO relapsed subgroup K-M analysis was based

on a small number of patients and had changing trajectory rendering interpretation problematical; at one year about 42% were FF-free, there is not data from the submission available beyond one year.

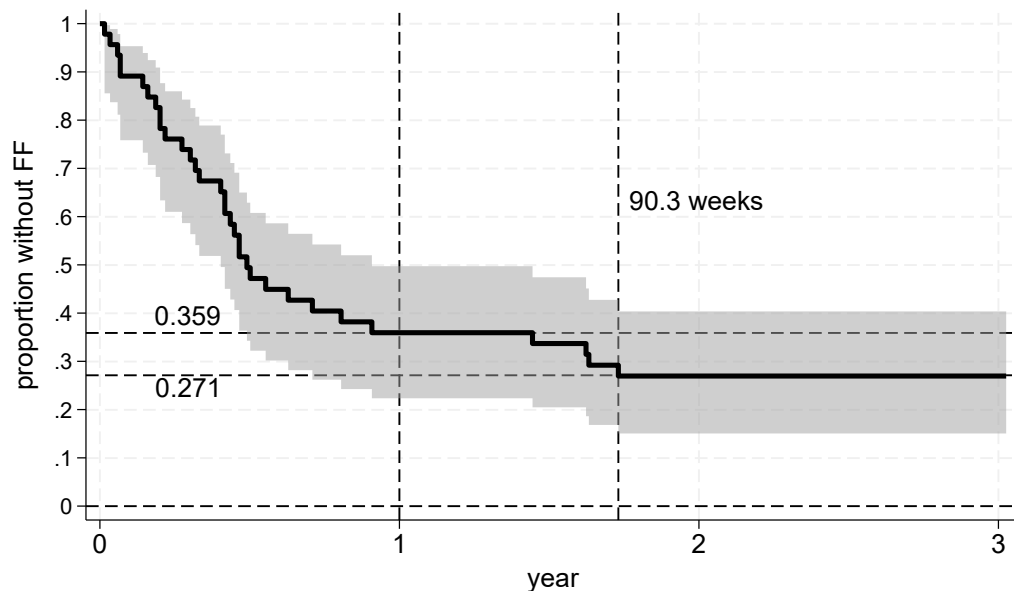


Figure 18: Reconstructed PBO K-M for the new onset subgroup of GiACTA followed for 3 years

Figure 25 shows the reconstructed KM plots for the GiACTA 3-year study PBO and tocilizumab comparing TTFF according to intervention (PBO versus tocilizumab) and subgroup (new-onset and relapsing). PBO and tocilizumab effectiveness are well separated while patients are still at risk of FF and differences between new-onset and relapsing subgroups are small within each intervention. A notable feature of the results is the consistent trajectory seen for both subgroups for both interventions. This contrasts with the changing trajectory for the PBO subgroups in SELECT-GCA trial (Figure 25).

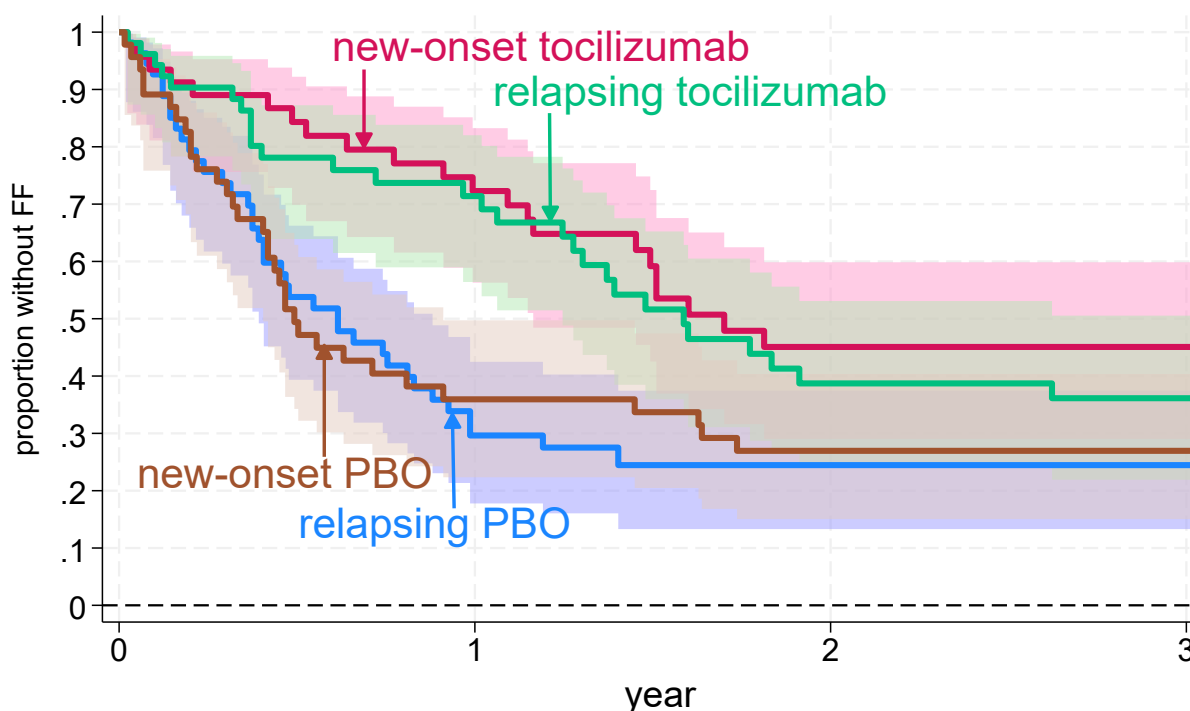


Figure 19: GiACTA K-M plots: comparison of tocilizumab versus PBO according to subgroup.

2.5.1.6 ITT populations SELECT-GCA and GiACTA studies: TTFF

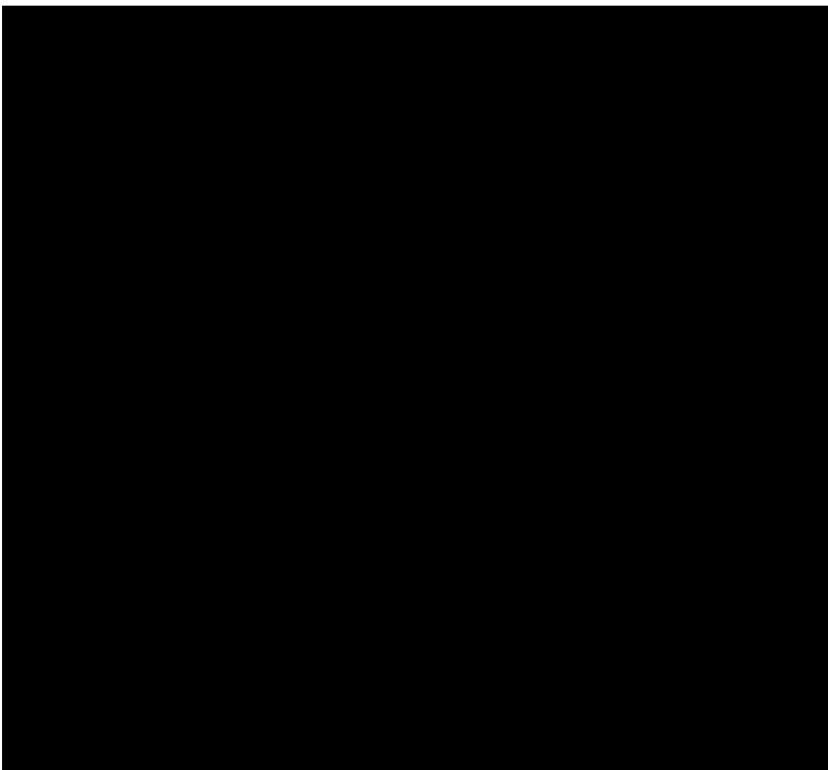
Given that the NICE scope listed tocilizumab as a comparator for upadacitinib and since the company submitted no information about tocilizumab for GCA treatment the EAG considered information on a comparison between these interventions to be informative and of potential relevance. An adjusted indirect treatment analysis was undertaken (section 2.5.2) and in the following section available IPD was used to make a comparison of TTFF between four treatments: upadacitinib vs. PBO from SELECT-GCA and tocilizumab vs. PBO from GiACTA.

Reconstructed IPD for the GiACTA ITT population was generated by combining subgroup IPD for PBO and tocilizumab using reconstructed IPD from the 3-year study of Stone 2022. GiACTA 3-year data for PBO encompassed pooled 26-week and 52-week steroid tapering regimens. EAG's clinical advisor's opinion suggests that in UK practice CS tapering will vary by clinicians' assessment of signs and symptoms of GCE; therefore pooling may encompass UK practice. Similarly, the tocilizumab data encompassed both TCZ QW (N=100) and TCZ Q2W (N=49) regimens, TCZ QW contributing twice as many patients as TCZ Q2W. Figures 1B

and 1C in Stone 2022 show that in both new-onset and relapsed subgroups TTFF is superior for the larger (N=100) TCZ QW and will dominate an ITT population derived from combining subgroups.

Baseline demographic differences between regimens and subgroups in GiACTA are considered in EAG section 2.5.2 “Adjusted indirect comparison between upadacitinib and tocilizumab” for the TCZ QW and PBO 52-week tapering groups. Similar differences will exist for the TCZ Q2W and PBO 26-week tapering groups.

The AbbVie base case economic analysis is conceptualised as upadacitinib with 26-week steroid tapering versus PBO with 52-week steroid tapering for all GCA patients irrespective of new-onset or relapsed condition using IPD from SELECT-GCA. There are multiple differences in IPD K-M analyses between subgroups and between treatments with considerable overlap of 95% CIs that indicate melding subgroups into the ITT population generates rather eccentric KM trajectory for the PBO population [REDACTED]; see also [REDACTED] [new-onset] and [REDACTED] [relapsed]).



■■■■■ shows the Kaplan-Meier plots for intervention (tocilizumab and upadacitinib) and PBO from the SELECT-GCA and GiACTA studies. Upadacitinib and tocilizumab plots are similar over one year while there is a large difference between PBO plots from the two studies. While acknowledging small sample sizes of the trials and inability to adjust for differences in prognostic factors, the comparison between the corrected IPD from AbbVie submission for the ITT population versus the 3-year GiACTA study of Stone 2022 imply that an advantage of active intervention over PBO (area between KM plots) is much greater for tocilizumab than for upadacitinib.



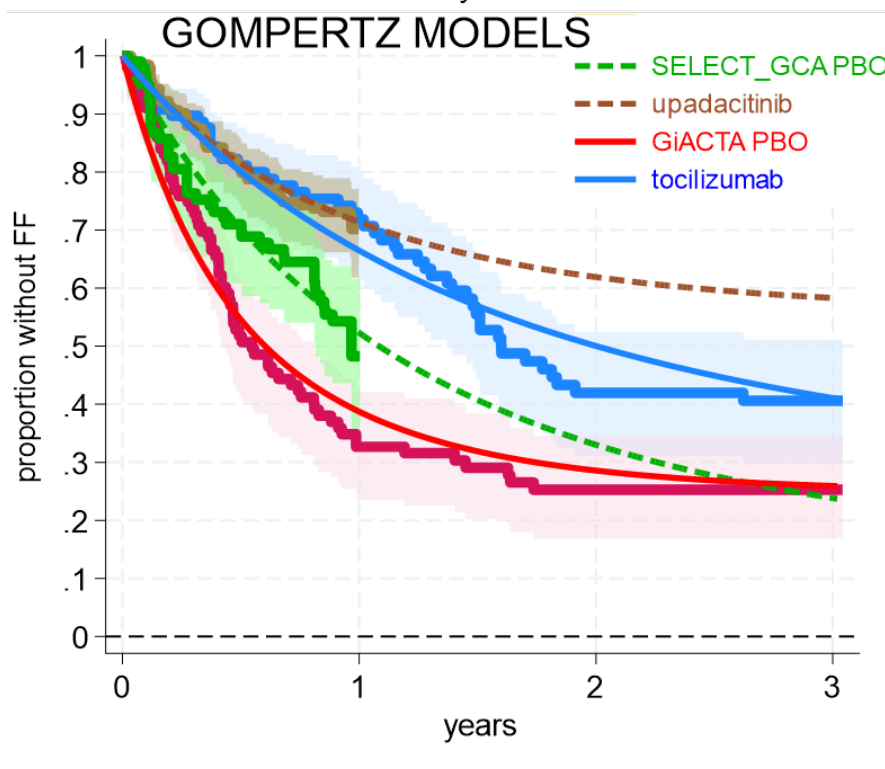
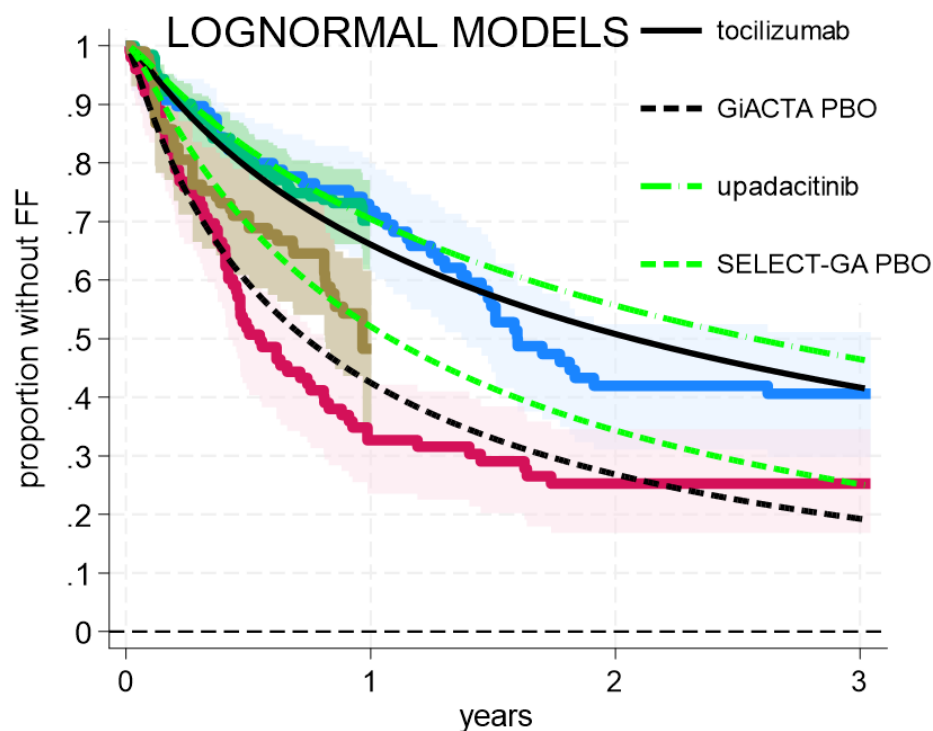
Unadjusted hazard ratios of intervention vs. PBO were: 0.503 (0.305 to 0.816) for SELECT-GCA and 0.508 (0.353 to 0.732) for GiACTA

Restricted mean survival values estimated for intervention versus control at 50, 104, and 156 weeks are summarised in Table 11. These suggest that over 50 weeks tocilizumab gains 11.5 weeks more mean survival than PBO while upadacitinib only gains 5.02 weeks more than PBO.

Table 11: Estimates of restricted mean survival, intervention versus PBO

WEEKS	SELECT_GCA upadacitinib	SELECT_GCA pbo	<i>Difference (upadacitinib minus pbo)</i>	GiACTA tocilizumab	GiACTA pbo	<i>Difference (tocilizumab minus pbo)</i>
50	36.6 (32.9-40.2)	41.6 (39.4-43.8)	5.0 (0.7-9.3)	41.8 (38.7-45.0)	30.4 (26.8-33.9)	11.5 (6.8-16.2)
104	ND	ND	ND	72.3 (64.8-79.8)	46.2 (38.3-54.0)	26.14 (15.3-37.0)
156	ND	ND	ND	93.0 (80.9-105.2)	58.8 (46.8-70.8)	34.3 (17.2-51.3)

To make comparisons beyond one year it is necessary to use extrapolated parametric models since the SELECT-GCA observed data only extends to one year. Lognormal and Gompertz parametric models were those favoured in the AbbVie submission for the ITT population. Figure 28 shows for lognormal and Gompertz models fit to SELECT-GCA and GiACTA intervention and control arms extrapolation to 3 years.



Kaplan-Meir (KM) plots are solid stepped lines. Upper panel: solid black line tocilizumab; long-dash green line SELECT-GCA Upadacitinib; short-dash green line SELECT-GCA PBO; dash black line GiACTA PBO. Lower panel: brown dash line SELECT-GCA Upadacitinib; blue solid line GiACTA tocilizumab; dash green line SELECT-GCA PBO; red solid line GiACTA PBO

Figure 20: SELECT-GCA (upadacitinib vs PBO) and GiACTA (tocilizumab vs PBO) ITT populations: Kaplan-Meier graphs with Lognormal (upper panel) and Gompertz (lower panel) models extrapolated to 3 years

Table 12 summarises estimates of the AUC for each lognormal model over 1 and 3 years.

Over 50 and 156 weeks lognormal models generate more benefit from tocilizumab versus placebo than from upadacitinib versus placebo.

Table 12 AUC estimates for lognormal models of ITT intervention and placebo treatments

WEEKS	SELECT-GCA upadacitinib	SELECT-GCA pbo	<i>Difference (upadacitinib minus pbo)</i>	GiACTA tocilizumab	GiACTA pbo	<i>DIFFerence (tocilizumab minus pbo)</i>
50	44.3	38.2	4.1	42.7	33.7	9.0
156	103.5	75.4	28.1	96.9	63.0	33.9

Table 13 summarises corresponding results for Gompertz models; over 50 weeks AUC values are like lognormal models but when Gompertz models are extended to 3 years they predict slightly more gain for upadacitinib over placebo (35.4 weeks) than tocilizumab over placebo (34 weeks). Figure 10 shows that from ~ 6 years to end of life the upadacitinib Gompertz model predicts no occurrence of FF and that after an assumed two-year treatment period effectiveness of the intervention apparently does not deteriorate.

Table 13: AUC estimates for Gompertz models of ITT intervention and placebo treatments.

WEEKS	SELECT-GCA upadacitinib	SELECT-GCA pbo	<i>Difference (upadacitinib minus pbo)</i>	GiACTA tocilizumab	GiACTA pbo	<i>DIFFerence (tocilizumab minus pbo)</i>
50	44.0	38.3	5.7	43	31.5	11.5
156	109.8	74.5	35.4	96.6	62.6	34

In summary the results from the EAG comparison between four treatment arms from SELECT-GCA and GiACTA trials suggest that superior effectiveness tocilizumab over upadacitinib cannot be ruled out; a similar conclusion to that reached from the EAG indirect adjusted treatment analysis (section 2.5.2).

2.5.2 Adjusted indirect comparison between upadacitinib and tocilizumab

Given the complete absence of evidence on relative effectiveness between upadacitinib and tocilizumab in the CS, the EAG carried out adjusted indirect comparisons of estimated treatment effects between upadacitinib and tocilizumab based on available data from their respective pivotal trial using the standard method suggested by Bucher et al,⁶³ with treatment effects anchored through the placebo arm of each trial. Comparison of baseline participant characteristics between SELECT-GCA for upadacitinib and GiACTA for tocilizumab (both for [expected] licensed dose against 52-week steroid tapering) is shown in Table 14.

Despite inevitable differences in the trial populations the EAG considers them to be broadly similar, and the analyses presented to be relevant for this appraisal.. A higher proportion of participants in SELECT-GCA had newly diagnosed GCA (about two-thirds) compared with participants in GiACTA (about half). Participants of SELECT-GCA had higher prevalence of cranial symptoms, lower prevalence of PMR symptoms, a shorter duration since diagnosis and a [REDACTED] proportion in remission at baseline compared with participants in the GiACTA trial. The company indicated in the FAC that the criteria for remission were less strict in SELECT-GCA.

Table 14: Demographic and disease characteristics for study participants at baseline: SELECT-GCA vs GiACTA

Study	SELECT-GCA		GiACTA	
Treatment arm	Upadacitinib 15 mg daily+ 26-week steroid taper (n=209)	Placebo + 52-week steroid taper (n=112)	Tocilizumab weekly + 26-week steroid taper (n=100)	Placebo + 52-week steroid taper (n=51)
Mean age (SD), yr	70.8 (7.3)	71.6 (7.3)	69.5 (8.5)	67.8 (7.7)
Female, % (n/N)	75% (156/209)	69% (77/112)	78% (78/100)	73% (37/51)
Race, % (n/N)				
White	95% (199/209)	92% (103/112)	97% (97/100)	96% (49/51)
Black	0% (0/209)	2% (2/112)	1% (1/100)	4% (2/51)
Asian	5% (10/209)	5% (6/112)	0% (0/100)	0% (0/51)
Other	0% (0/209)	0% (0/112)	1% (1/100)	0% (0/51)
Unknown	0% (0/209)	0% (0/112)	1% (1/100)	0% (0/51)
Mean weight (SD), kg	69.0 (16.0) ^a	71.1 (16.0)	69.8 (13.8)	73.1 (15.3)
Disease status, % (n/N)				
Newly diagnosed	71% (148/209)	68% (76/112)	47% (47/100)	45% (23/51)
Relapsing disease	29% (61/209)	32% (36/112)	53% (53/100)	55% (28/51)
Mean corticosteroid dose (SD), mg	34.6 (12.7)	34.6 (11.9)	NR	NR
Baseline corticosteroid dose ≤30 mg	53% (110/209)	53% (59/112)	52% (52/100)	51% (26/51)
Mean duration since diagnosis (SD), days	222 (467)	240 (545)	307 (564)	255 (436)
Mean ESR (SD), min/hr	19.5 (17.5)	21.7 (25.5) ^b	24.6 (18.7)	24.2 (18.2)
Cranial symptoms, % (n/N)	93% (194/209)	84% (94/112)	78% (78/100)	78% (40/51)

Symptoms of PMR	52% (109/209)	62% (69/112)	59% (59/100)	69% (35/51)

In remission	■ ^c	■ ^c	55% ^d	51% ^d

ESR: erythrocyte sedimentation rate; NR: not reported; PMR: polymyalgia rheumatica

^a n=207; ^b n=111; ^c SELECT-GCA Clinical Study Report; ^d NICE committee paper TA518

Data source: CS & Stone et al. 2017⁶⁴

Acknowledging the limited statistical power in relation to relatively small sample sizes of the trials and inability to adjust for some potential differences in prognostic factors between trial participants the EAG undertook two sets of adjusted indirect comparisons: one was based on reported risk ratios and hazard ratios for outcomes related to remission/flare; the other was based on reconstructed K-M plots for time to first flare reported in SELECT-GCA and GiACTA trials. The findings are reported in the following subsections.

2.5.2.1 Adjusted indirect comparisons based on risk ratios and hazard ratios

Findings based on risk ratios and hazard ratios reported in the two pivotal trials are shown in Table 15. The results indicated that a difference in effectiveness in favour of tocilizumab cannot be ruled out based on relapse/remission related outcomes. The findings were consistent across new onset and relapsing patient subgroups. Data contributing to the adjusted indirect comparisons are shown in ■ and Figure 30.

Table 15: Adjusted indirect comparison for upadacitinib vs tocilizumab

RR (95% CI)	Direct comparison (SELECT -GCA)	Direct comparison (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	■	2.74 (1.22 to 6.16)	■
Relapsing	■	3.70 (1.44 to 9.49)	■

Experiencing at least 1 flare by week 52 (Risk ratio)

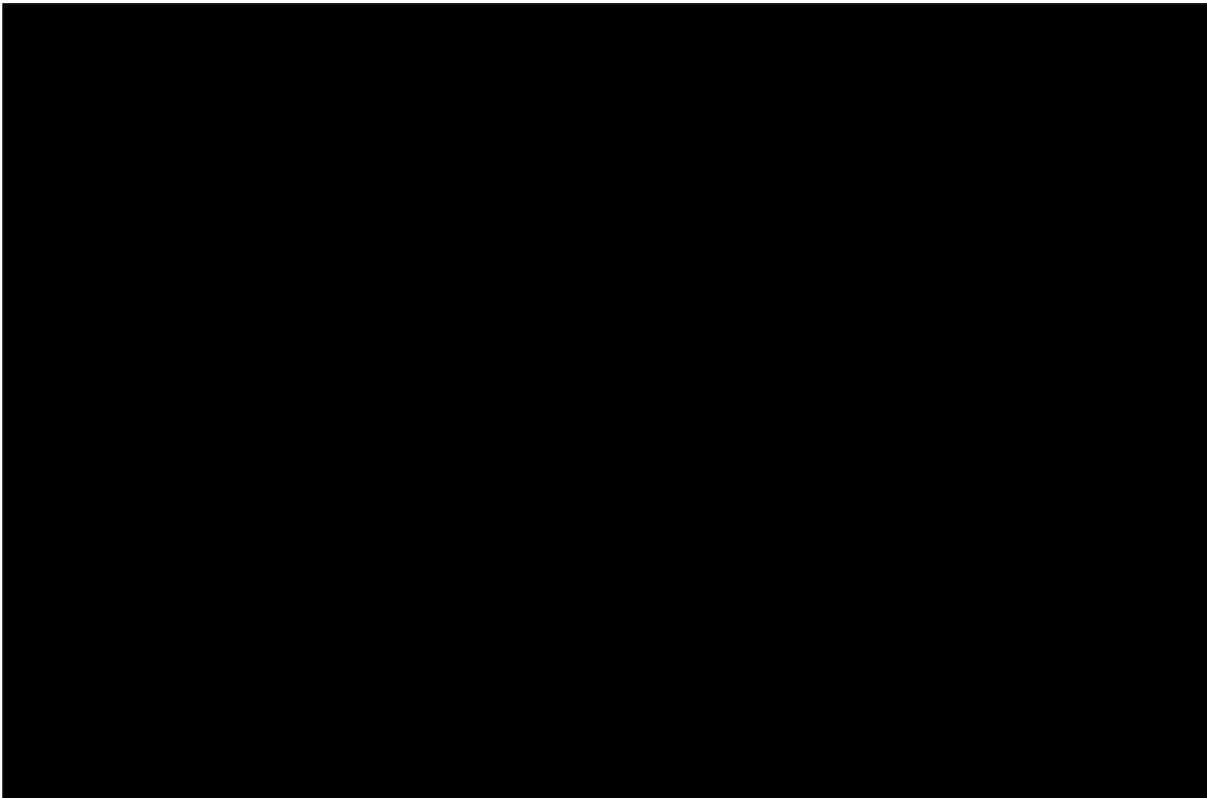
ITT 0.62 (0.48 to 0.80) 0.47 (0.30 to 0.74) 1.32 (0.79 to 2.22)

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



21

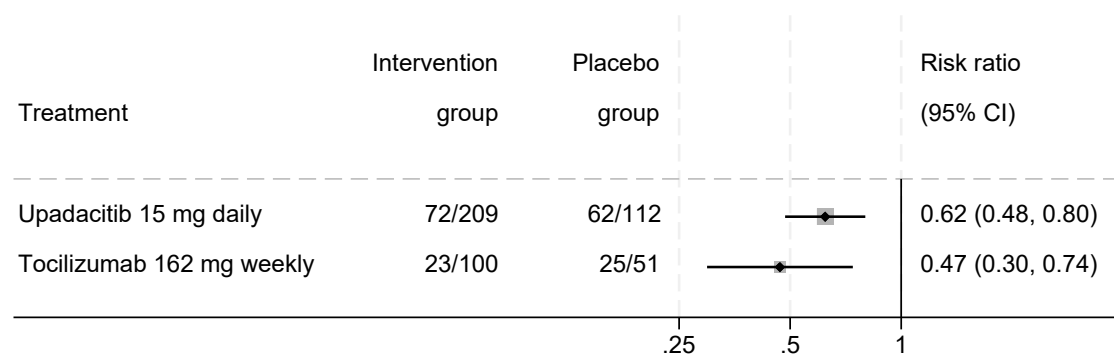


Figure 22: Experiencing at least one flare at week 52 – results from SELECT-GCA and GiACTA trials ITT population

Data on cumulative steroid doses recorded in the two trials are shown in Table 16. Participants receiving both treatments had lower cumulative steroid dose compared with corresponding placebo groups

Table 16: Comparative data for cumulative steroid dose from SELECT-GCA and GiACTA trial

Study	SELECT-GCA		GiACTA	
Outcome	Upadacitinib 15 mg daily+ 26-week steroid taper (n=209)	Placebo + 52-week steroid taper (n=112)	Tocilizumab weekly + 26-week steroid taper (n=100)	Placebo + 52-week steroid taper (n=51)
New on-set GCA				
Cumulative CS dose (mg): median (95% CI)			1,942 (1,822 to 2,519)	3,817 (2,578 to 4,585)
Relapsing patients				
Cumulative CS dose: median (95% CI)			1,385 (1,127 to 1,862)	3,785 (2,223 to 5,373)

2.5.2.2 Adjusted indirect comparisons based on reconstructed K-M plots

2.5.2.2.1 GiACTA tocilizumab and SELECT-GCA upadacitinib versus placebo: 52-week data

The EAG conducted an adjusted indirect comparison of tocilizumab versus upadacitinib using 52-week data from GiACTA⁶⁴ and SELECT-GCA studies. Figure 31 shows reconstructed ITT KM plots for tocilizumab QW 26wk CST (N=100) and placebo with 56wk CST (N=51). Figure 32 shows the corresponding Kaplan-Meier analyses for the ITT population from SELECT-GCA.

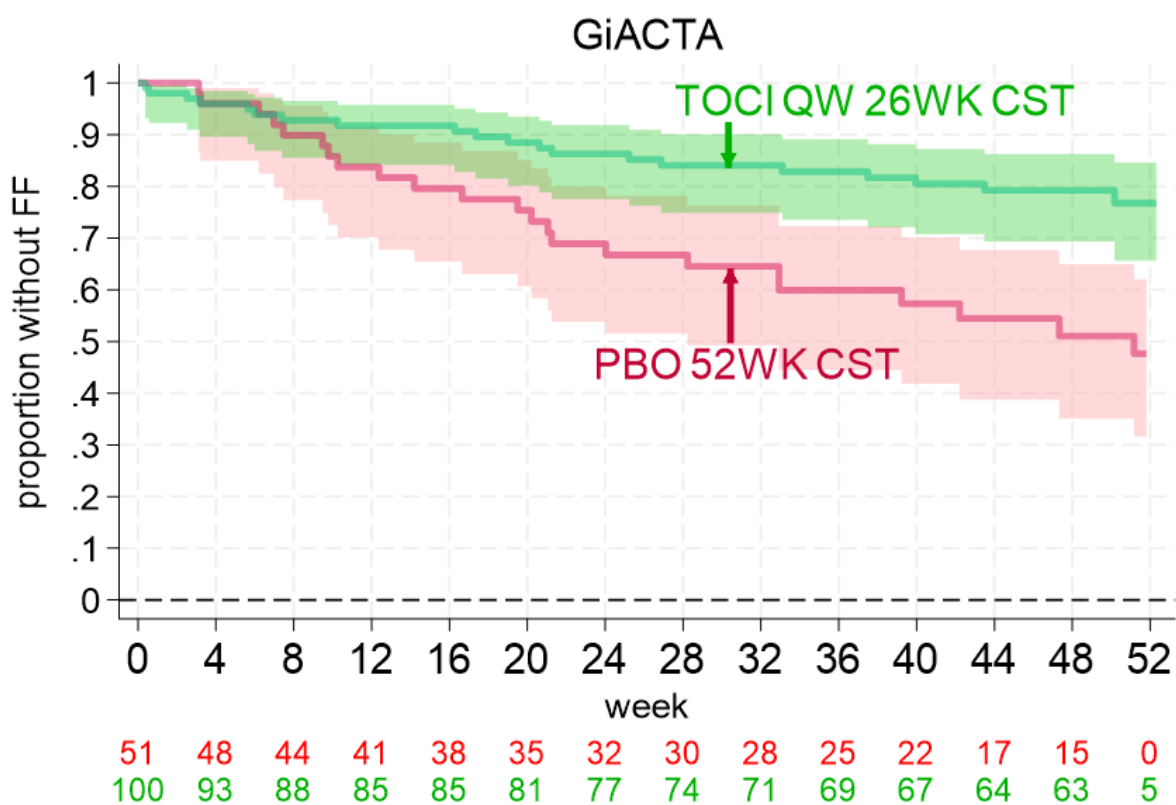


Figure 23: Reconstruct Kaplan-Meier plots based on GiACTA 52 weeks observed TTFF

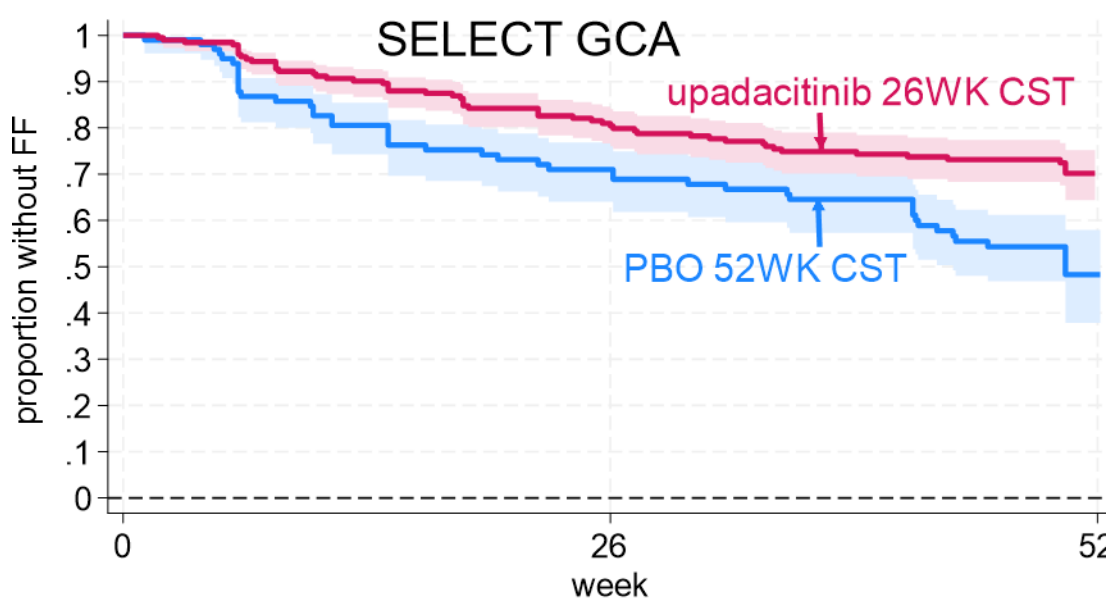


Figure 24: Kaplan-Meier plots based on SELECT-GCA 52 weeks observed TTFF

Table 17 summarises EAG estimates of restricted mean survival to 51 weeks for each of the Kaplan-Meier plots shown in Figure 31 and Figure 32.

Table 17: Restricted mean survival estimates to 51 weeks according to intervention and trial

<i>ITT SELECT GCA</i>			
	PBO 52wk CST	UPADAC 26wk CST	<i>INTERVENTION-CONTROL</i>
51 wks	37.08 (33.3-40.8)	42.3 (40.0-44.6)	5.23 (0.8-9.6)
<i>ITT GiACTA</i>			
	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)

Despite absence of adjustment for covariant differences these estimates are consistent with superior performance for tocilizumab relative to upadacitinib. The difference between tocilizumab and upadacitinib is sufficiently large to infer that inferiority of upadacitinib cannot be ruled out.

The company submission favours lognormal and Gompertz models for extrapolation beyond the observed data. Figure 33 and Figure 34 respectively show lognormal and Gompertz models fit to GiACTA and SELECT-GCA 52-week data extrapolated to 3-years.

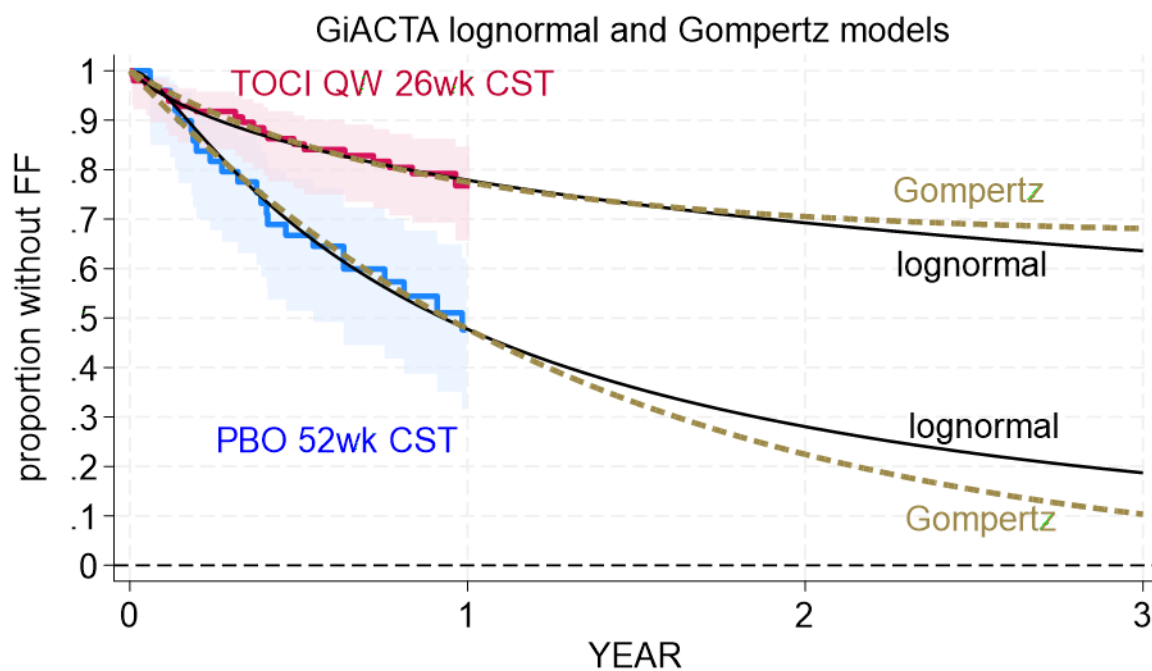


Figure 25: Lognormal and Gompertz models fit to intervention and control arms of GiACTA

Lognormal and Gompertz models from GiACTA are the same over the observation period and differ only slightly in extrapolation.

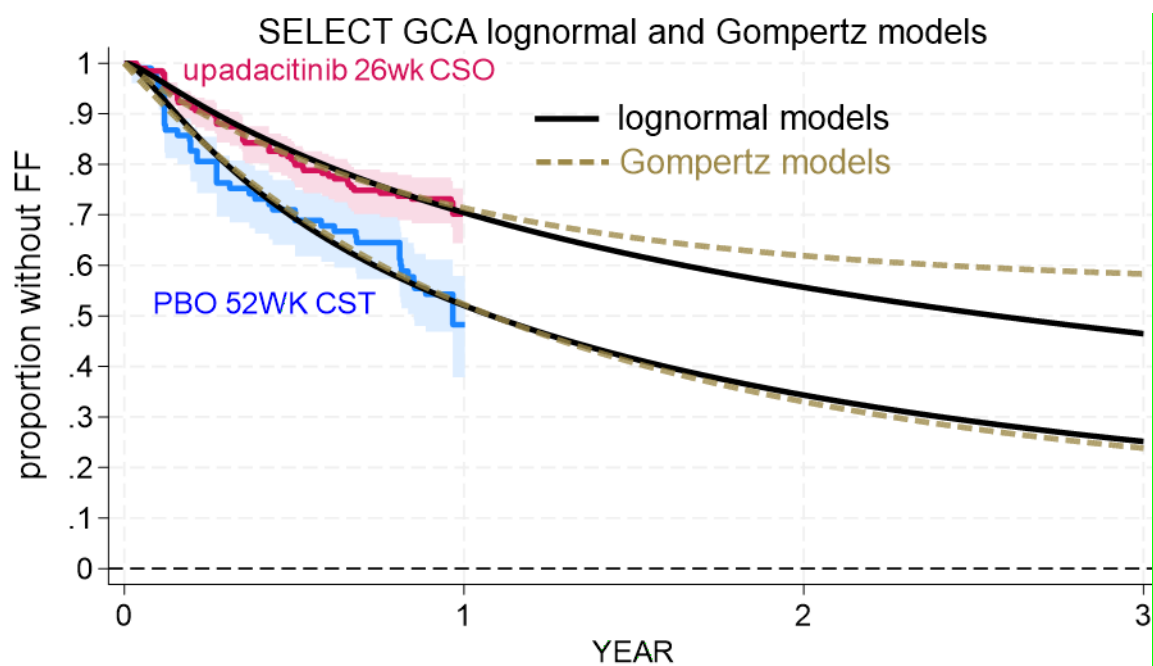


Figure 26: Lognormal and Gompertz models fit to intervention and control arms of SELECT-GCA

Lognormal and Gompertz models from SELECT GCA are the same over the observation period and present poor visual fit to the PBO observed KM plot. In extrapolation lognormal and Gompertz models for the visually poor fit for PBO are almost identical while in contrast there is a substantial difference between models for the upadacitinib arm where the Gompertz model implies that nearly 60% of patients will not experience FF during their lifetime while the PBO Gompertz model predicts continuing occurrence of FF during lifetime.

Table 18 and Table 19 summarise AUC estimates of benefit from lognormal and Gompertz models for TTFF using GiACTA and SELECT GCA 52-week data.

Lognormal models suggest more benefit from tocilizumab than upadacitinib after both 1 year and three years. In contrast Gompertz models suggest greater benefit from upadacitinib than tocilizumab that is driven by the Gompertz model for the upadacitinib arm that predicts lifelong exemption from FF for nearly 60% of patients from about 3 years onward.

Table 18: AUC estimates for lognormal models of ITT intervention and placebo

WEEKS	<i>SELECT_GCA upadacitinib</i>	<i>SELECT_GCA pbo</i>	<i>Difference (upadacitinib minus pbo)</i>	GiACTA tocilizumab	GiACTA pbo	<i>DIFFerence (tocilizumab minus pbo)</i>
52	44.3	38.2	4.1	42.7	33.7	9.0
156	103.5	75.4	28.1	96.9	63.0	33.9

Table 19: AUC estimates for Gompertz models of ITT intervention and placebo

WEEKS	<i>SELECT_GCA upadacitinib</i>	<i>SELECT_GCA pbo</i>	<i>Difference (upadacitinib minus pbo)</i>	GiACTA tocilizumab	GiACTA pbo	<i>DIFFerence (tocilizumab minus pbo)</i>
52	43.9	38.3	15.6	43.0	31.5	11.5
156	109.8	74.6	35.2	96.6	62.6	30.0

In summary, the adjusted indirect comparison of results from 52-week observed data for the two trials suggest that inferiority of upadacitinib relative to tocilizumab cannot be ruled out.

2.5.2.2.2 GiACTA tocilizumab versus placebo: three-year data

Due to the complete absence of clinical effectiveness data beyond one year for upadacitinib, the EAG explored published longer-term data for tocilizumab for illustrative purposes. Several caveats are related to the analyses presented below are acknowledged, including the combination of sub-licensed dose with licensed dose for tocilizumab; the combination of 52-week steroid tapering with 26-week steroid tapering for the control group (the latter being generally considered too aggressive); and that participants in the placebo groups could receive tocilizumab after year 1 and therefore the observed clinical outcomes no longer reflected steroid-only treatment.

The EAG reconstructed three-year IPD and KM for relapsing and new onset PBO subgroups reported by Stone 2022⁶² in which 26- and 52- week tapering PBO groups and the tocilizumab dose regimens (QW and 2QW) were each pooled. Figure 35 shows results for the relapsing subgroup (N=55). After 72.9 weeks 24.5% of relapsing subgroup remain without an FF event for a further 83.6 weeks. At one year approximately 30% remain without FF. The AbbVie PBO relapsing subgroup K-M at approximately 1 year indicates just over 50% without FF; maintenance of this proportion beyond one year is unknown and can only be modelled using poor visual fit parametric models guided by clinical opinion.

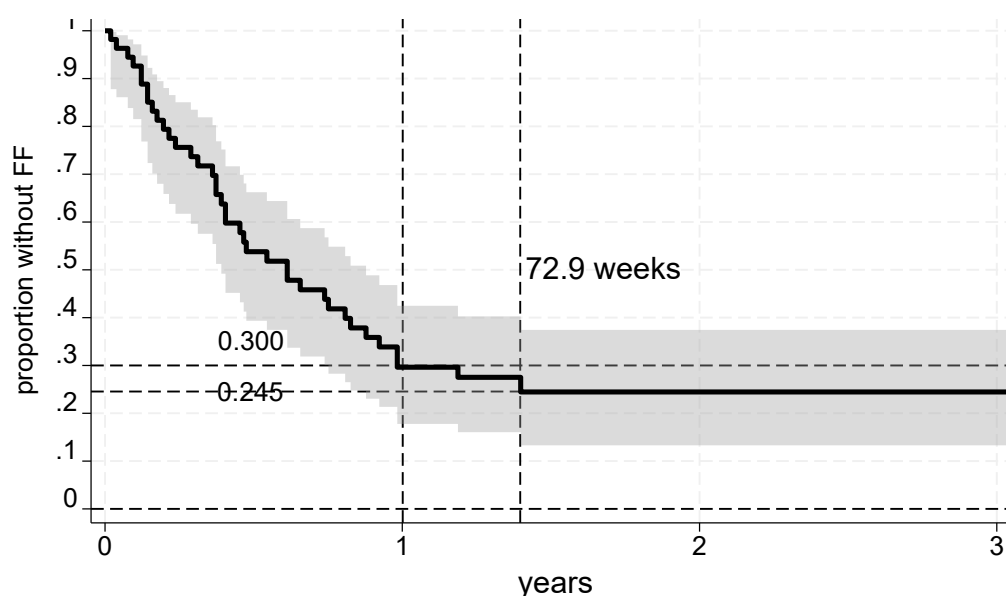


Figure 27: Reconstructed PBO K-M for the relapsing subgroup of GiACTA followed for 3 years

Figure 36 shows GiACTA PBO TTFF results for the new onset subgroup (N=46). After 90.3 weeks 27.1% of new onset subgroup remain without an FF event for a further 66.3 weeks. At one year approximately 35.9% remain without FF. The AbbVie PBO new onset subgroup K-M at approximately 1 year indicates just over 50% without FF; maintenance of this proportion beyond one year is unknown and can only be modelled using poor visual fit parametric models guided by clinical opinion. Figure 36 also shows that from about 1.7 years to 3 years about 24% of new onset remain FF-free. The AbbVie PBO relapsed subgroup K-M analysis was based on a small number of patients and had changing trajectory rendering interpretation problematical; at one year about 42% were FF-free, there is no data from the AbbVie submission available beyond one year.

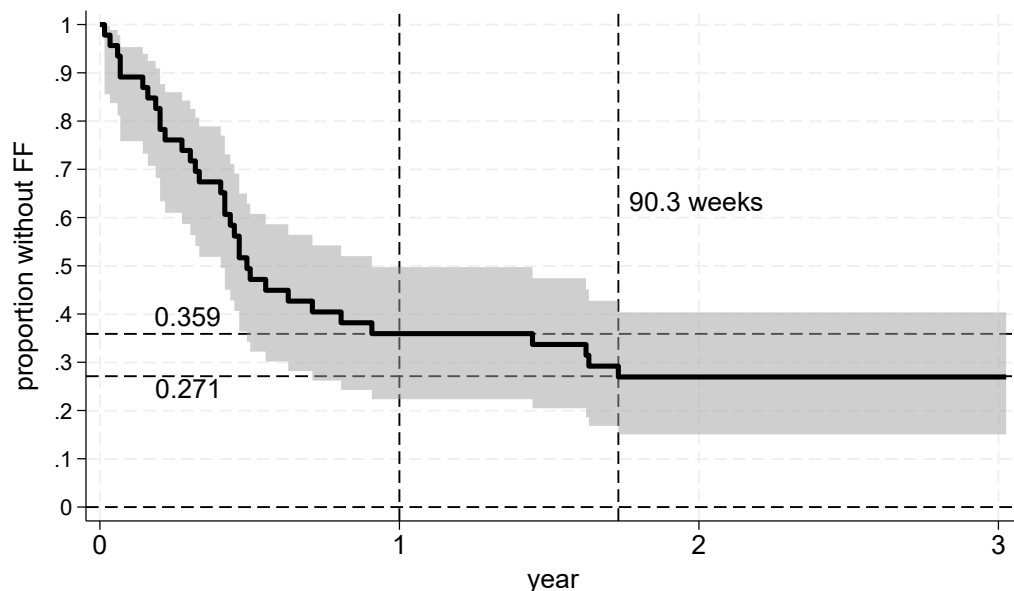


Figure 28: Reconstructed PBO K-M for the new onset subgroup of GiACTA followed for 3 years

Figure 37 shows the reconstructed KM plots for the GiACTA 3-year study PBO and tocilizumab comparing TTFF according to intervention (PBO versus tocilizumab) and subgroup (new-onset and relapsing). PBO and tocilizumab effectiveness are well separated while patients are still at risk of FF and differences between new-onset and relapsing subgroups are small within each intervention. A notable feature of the results is the consistent trajectory seen for both subgroups for both interventions. This contrasts with the changing trajectory for the PBO subgroups in SELECT-GCA trial.

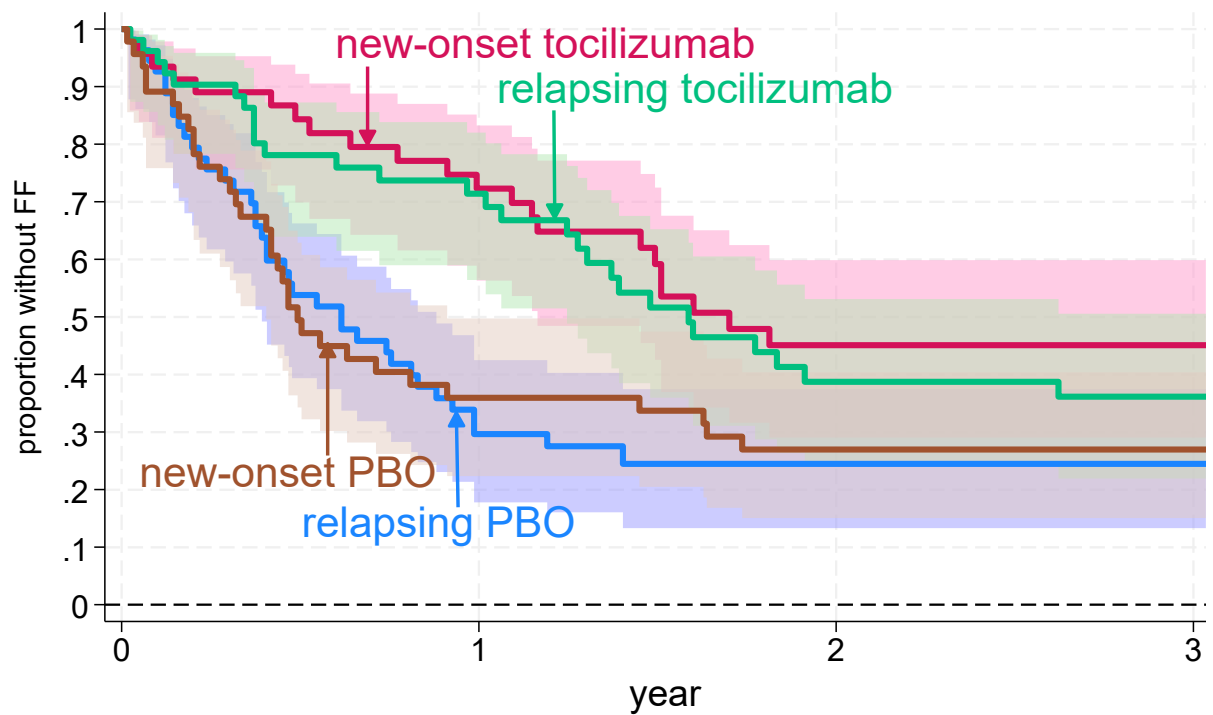


Figure 29: GiACTA K-M plots: comparison of tocilizumab versus PBO according to subgroup

Reconstructed IPD for the GiACTA ITT population was generated by combining subgroup IPD for PBO and tocilizumab using reconstructed IPD from the 3-year study of Stone 2022. GiACTA 3-year data for PBO encompassed pooled 26-week and 52-week steroid tapering regimens. EAG's clinical advisor's opinion suggests that in UK practice CS tapering will vary by clinicians' assessment of signs and symptoms of GCE; therefore pooling may encompass UK practice. Similarly, the tocilizumab data encompassed both TCZ QW (N 100) and TCZ Q2W (N=49) regimens, TCZ QW contributing twice as many patients as TCZ Q2W. Figures 1B and 1C in Stone 2022 show that in both new-onset and relapsed subgroups TTFF is superior for the larger (N=100) TCZ QW and will dominate an ITT population derived from combining subgroups. Baseline demographic differences between regimens and subgroups in GiACTA are considered in EAG section "*Adjusted indirect comparison between upadacitinib and tocilizumab*" for the TCZ QW and PBO 52-week tapering groups. Similar differences will exist for the TCZ Q2W and PBO 26-week tapering groups.

The AbbVie base case economic analysis is conceptualised as Upadacitinib with 26-week CS tapering versus PBO with 52-week CS tapering for all GCA patients irrespective of new-onset or relapsed condition using IPD from SELECT-GA. There are multiple differences in IPD K-M analyses between subgroups and between treatments with considerable overlap of 95% CIs that indicate melding subgroups into the ITT population generates rather eccentric KM trajectory for the PBO population [REDACTED]

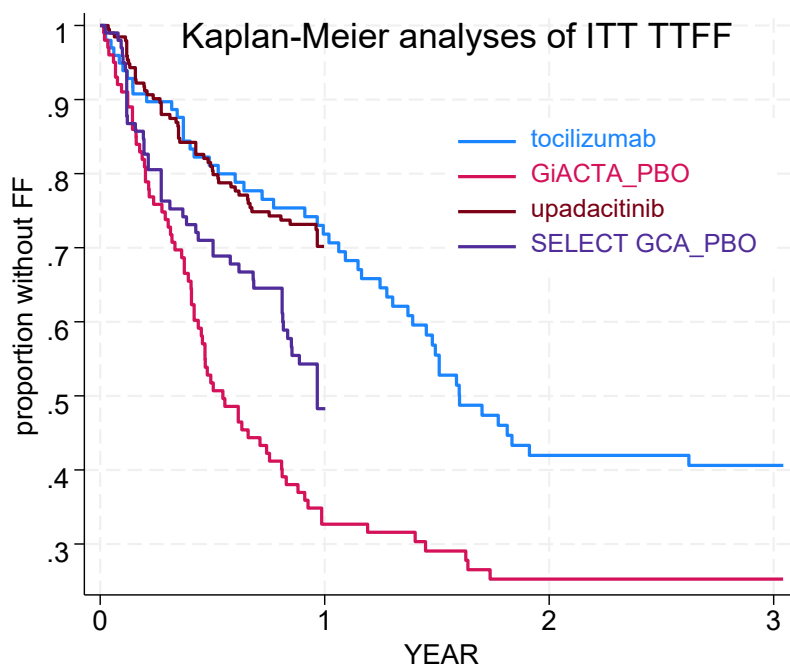


Figure 30: Kaplan-Meier analyses of TTFF for Select GA and GiACTA ITT populations

Unadjusted hazard ratios of intervention vs. PBO were: 0.503 (0.305 to 0.816) for SELECT-GCA and 0.508 (0.353 to 0.732) for GiACTA.

Figure 39 shows the Kaplan-Meier plots for intervention (tocilizumab and upadacitinib) and PBO group from the SELECT-GCA and GiACTA. Upadacitinib and tocilizumab plots are similar over one year while there is a large difference between PBO plots from the two studies. An indirect comparison (adjusting for placebo group

response) between AbbVie ITT population and 3-year ITT GiACTA study implies that an advantage of active intervention over PBO (area between KM plots) is much greater for tocilizumab than for Upadacitinib. This is supported by restricted mean survival values estimated for intervention versus control at 50, 104, and 156 weeks as summarised in Table 20. These suggest that over 50 weeks tocilizumab gains 11.5 weeks more mean freedom from FF than PBO while Upadacitinib only gains 5.02 weeks more than PBO.

Table 20: Estimates of restricted mean survival, intervention versus PBO

WEEKS	SELECT_GCA upadacitinib	SELECT_GCA pbo	<i>Difference (upadacitinib minus pbo)</i>	GiACTA tocilizumab	GiACTA pbo	<i>Difference (tocilizumab minus pbo)</i>
50	36.6 (32.9-40.2)	41.6 (39.4-43.8)	5.02 (0.74- 9.30)	41.8 (38.7- 45.0)	30.4 (26.8- 33.9)	11.5 (6.8-16.2)
104	ND	ND	ND	72.3 (64.8- 79.8)	46.2 (38.3- 54.0)	26.14 (15.3- 37.0)
156	ND	ND	ND	93.0 (80.9- 105.2)	58.8 (46.8- 70.8)	34.3 (17.2- 51.3)

To make comparisons beyond one year it is necessary to use extrapolated parametric models since AbbVie data is for 52 weeks only. Figure 40 shows lognormal and Gompertz models extrapolated to 3 years.

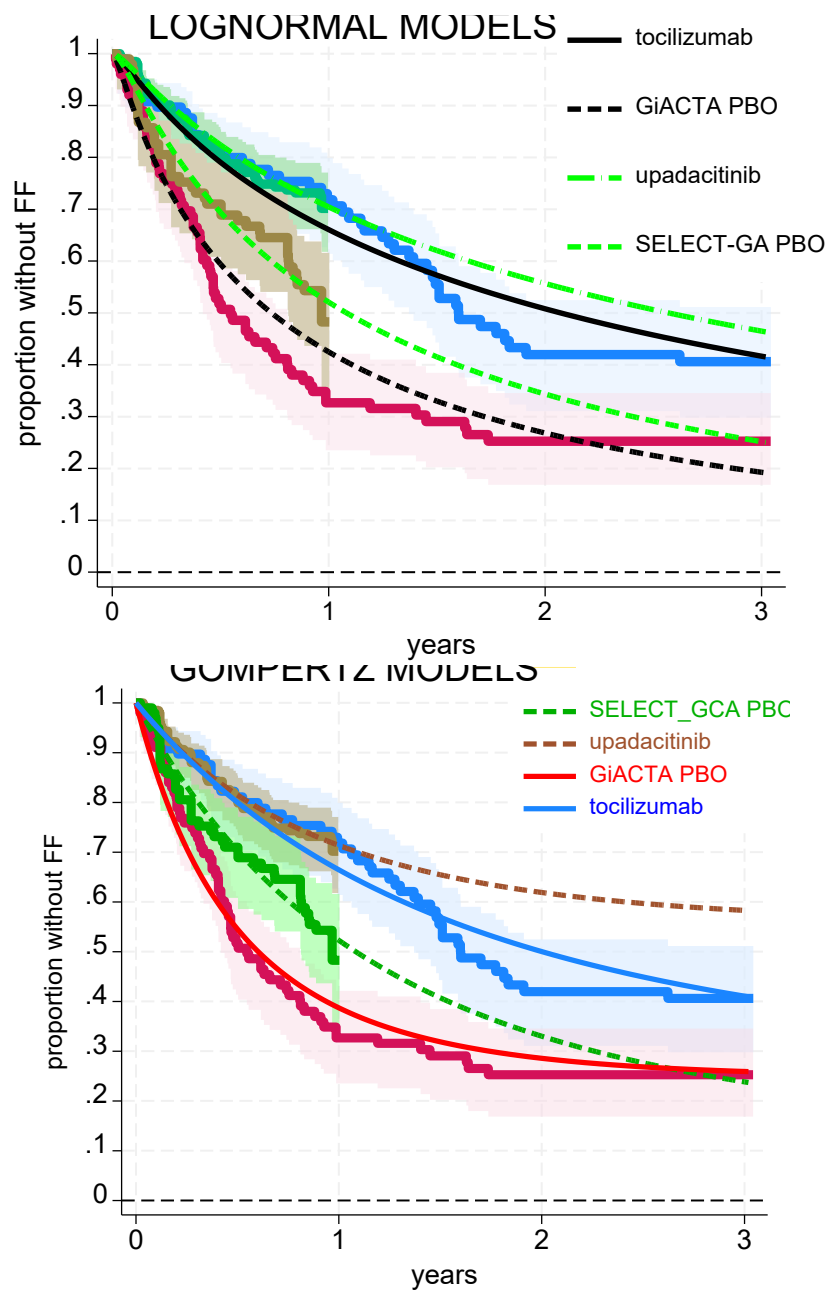


Figure 31: Select GCA and GiACTA ITT populations: Lognormal and Gompertz models extrapolated to 3 years

Table 21 summarises estimates of the AUC for each lognormal model over 1 and 3 years.

Lognormal models generate more benefit from tocilizumab versus placebo than from upadacitinib versus placebo.

Table 21: AUC estimates for lognormal models of ITT intervention and placebo treatments

WEEKS	SELECT_GCA upadacitinib	SELECT_GCA pbo	<i>Difference (upadacitinib minus pbo)</i>	GiACTA tocilizumab	GiACTA pbo	<i>DIFFerence (tocilizumab minus pbo)</i>
50	44.3	38.2	4.1	42.7	33.7	9.0
156	103.5	75.4	28.1	96.9	63.0	33.9

Table 22 summarises corresponding results for Gompertz models; over 50 weeks AUC values are like lognormal models but when Gompertz models are extended to 3 years they predict slightly more gain for upadacitinib over placebo (35.4 weeks) than tocilizumab over placebo (34 weeks). From ~ 6 years to end of life the upadacitinib Gompertz model predicts no occurrence of FF and that after only two-years treatment effectiveness of the upadacitinib apparently never deteriorates.

Table 22: AUC estimates for Gompertz models of ITT intervention and placebo treatments.

WEEKS	SELECT_GCA upadacitinib	SELECT_GCA pbo	<i>Difference (upadacitinib minus pbo)</i>	GiACTA tocilizumab	GiACTA pbo	<i>DIFFerence (tocilizumab minus pbo)</i>
50	44.0	38.3	5.7	43	31.5	11.5
156	109.8	74.5	35.4	96.6	62.6	34

In summary the results from the EAG indirect comparison adjusting for placebo response suggest that clinically relevant differences in effectiveness between tocilizumab and upadacitinib cannot be ruled out, and longer term data beyond 1 year will be crucial for a robust assessment.

2.6 Conclusions of the clinical effectiveness section

- The company submission did not include any comparative evidence between upadacitinib and tocilizumab, which is a treatment recommended by NICE for patients with relapsing/refractory GCA. EAG considered this to be a critical omission.
- Clinical effectiveness evidence for upadacitinib primarily came from the SELECT-GCA study, which was generally a well-conducted trial with low risk of bias and demonstrated superiority of upadacitinib 15 mg daily compared

with placebo in achieving sustained remission and other secondary effectiveness outcomes.

- Despite reduction in the exposure to cumulative steroid dose for upadacitinib treatment participants compared with placebo-treated participants, no significant difference in corticosteroid-related AEs were observed between treatment groups; the proportion of participants experiencing such AEs as judged by investigators was higher in the upadacitinib arm, casting doubt with regard to the actual benefit that could be realised by upadacitinib's steroid-sparing effect.
- For the key outcome of time to first flare, the company did not provide data beyond 52 weeks. EAG's exploration of K-M data provided by the company suggested that the available data were inadequate to allow reliable long-term extrapolation of the key effectiveness outcomes.

3 COST EFFECTIVENESS

3.1 EAG comment on company's review of cost-effectiveness evidence

The company's review of cost-effectiveness evidence was presented in CS Appendix E. In addition, the company also searched for and collated evidence from studies of health-related quality of life and studies of cost and healthcare resource identification, measurement and valuation in GCA population. These were described in CS Appendix F and G respectively. A brief critique of the company's relevant SLRs is provided below.

3.1.1 Search strategy

Searches were undertaken in May 2024 and updated in February 2025. An appropriate and broad range of databases, websites of HTA agencies and recent conference proceedings were searched. Reference checking of relevant systematic reviews was also undertaken. The database searches include database-specific indexing and free text terms for the condition and study types of interest. Omitting search terms for the intervention or comparator(s) increases the sensitivity of the searches. No language limits were applied and the searches were restricted to studies published after 2010. Justification for limiting to this year is not provided; however, a rapid test search carried out by the EAG revealed that this would not lead to potentially relevant results being missed. A single search strategy was used to retrieve studies to inform a SLR on cost effectiveness studies, health related quality of life (HRQoL) AND cost and healthcare resource identification, measurement and valuation (CS Appendix F, G and H). The company did not utilise recognised or validated search filters to restrict the searches to these study types. Additional search terms could have included (but not limited to) terms such as 'disutility/ies', 'decision tree/s' and 'economic modelling'. The EAG would recommend utilising search filters to restrict to cost, HRQoL and cost and healthcare resource identification, measurement and valuation searches to ensure comprehensiveness. The EAG ran targeted searches longitudinal/ natural history/ baseline events and standard mortality ratios studies (**Appendix 1: EAG searches**).

3.1.2 Study selection criteria, quality assessment and synthesis

The company's SLR adopted a broad scope, which covered all adults with GCA diagnosis with no restriction on interventions and comparators. Study design targeted various forms of full economic evaluation. Included studies were quality assessed using the Phillips checklist.⁶⁵ The SLR included 49 reports from 39 studies, of which 10 studies (10 reports) included cost-effectiveness evidence and were presented in CS Appendix E. The remaining studies/reports were presented in CS Appendix F and G.

Of the 10 cost-effectiveness studies, eight compared tocilizumab with (faster) steroid tapering versus steroid tapering alone. One study compared a fast-track pathway with traditional referral route for GCA,⁶⁶ while the other evaluated ultrasound versus temporal artery biopsy for the diagnosis and management of GCA.⁶⁷ Details of these studies can be found in CS Appendix E, Tables 87 and 88. No economic evaluation of upadacitinib was identified.

Similar to the company's SLR for clinical effectiveness evidence, the SLR for cost-effectiveness presented data from individual studies included in the review in the form of summary tables, but there was no further synthesis of the extracted data. There was no comparison or commentary with regard to the strengths, weaknesses and applicability of the presented evidence between and across studies. The SLR appears mainly as background with the company appearing to rely mainly upon the modelling and FAD of TA518 to inform its own de novo modelling. The same can be said for the additional evidence presented in CS Appendix F and G.

3.2 Summary and critique of the company's submitted economic evaluation by the EAG

3.2.1 NICE reference case checklist

Table 23: NICE reference case checklist

Element	Reference case	EAG comment
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	Yes.
Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. Lifetime.
Synthesis of evidence on health effects	Based on systematic review	The submission relies upon data from the first year Period 1 data of SELECT-GCA. This is coupled to a company analysis of a US health insurance database to estimate the effects of steroid use.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes. The standard UK tariff.

Element	Reference case	EAG comment
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

3.2.2 Model structure

The company model presents a de novo Markov model with a 1 week cycle length and numerous tunnel health states to account for steroid tapering of up to 52 weeks.

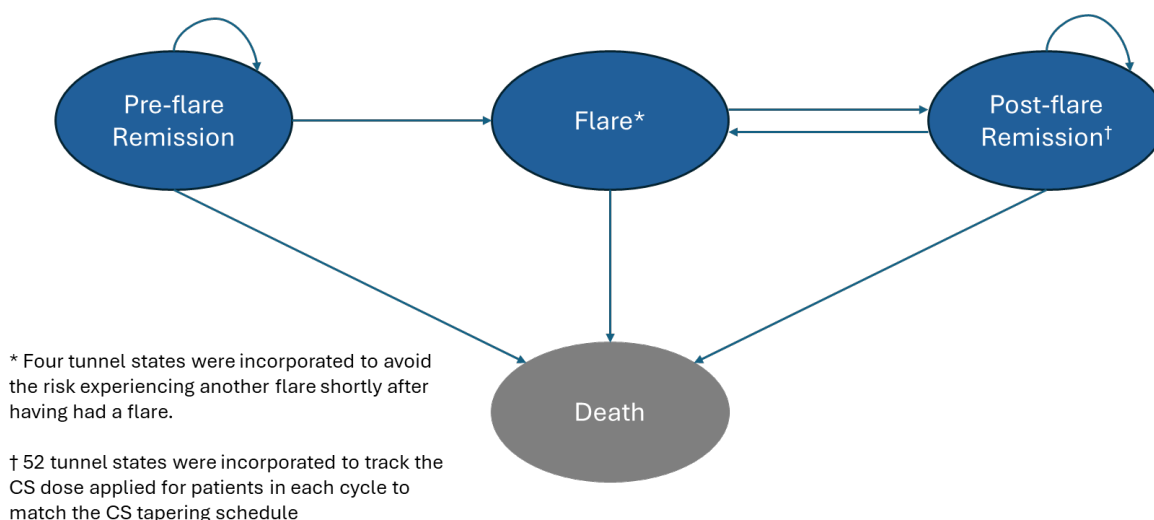


Figure 32: Company model structure: © AbbVie (2025)

The company compares:

- Upadacitinib with a 26-week steroid taper and a 2 year stopping rule, with
- Placebo and a 52-week steroid taper.

Patients start the model in remission and tapering steroids, the Kaplan Meier data censoring patients not in remission at baseline.

The risks of first flare are estimated by fitting the standard set of parameterised curves to SELECT-GCA Period 1 Kaplan Meier data, independently for the upadacitinib arm and the placebo arm. The company base case applies the log-normal for the ITT population. Subgroup modelling for the new onset applies the Gompertz, and for the relapsed applies the log-normal.

The risk of subsequent flares is estimated by fitting a Poisson distribution to SELECT-GCA Period 1 data, again independently for the upadacitinib arm and the placebo arm with population specific estimates for the ITT, the new onset and the relapsed.

There is a 2-year stopping rule for upadacitinib. When upadacitinib is stopped the placebo arm probabilities of first flare and subsequent flare are applied.

Standardised mortality ratios are drawn from the literature: 1.03 while in remission and 1.49 while in flare. These have little effect upon model outputs.

When patients flare, they enter the flare state and increase their steroid dose to the last previously used dose unless the flare is severe when a minimum daily dose of 40mg is assumed. While in flare patients are at risk of the GCA related complications of visual loss, aortic aneurism, aortic dissection, myocardial infarction and stroke. Flare lasts for four weekly cycles after which patients re-enter remission and recommence steroid tapering.

A key interim output of the modelling is the mean total steroid dose since baseline. This determines the risk of conditions which steroids can increase the risk of developing, such as osteoporosis. Crucial to understanding the model is that in each arm during each cycle there is only one mean cumulative steroid dose estimate.

While on upadacitinib patients can experience JAK related adverse events.

The main health states of remission and flare have quality of life values of 0.7685 and 0.7098 estimated from the SELECT-GCA trial.

Health state costs are estimated from the TA518 submission. Weekly costs are highest while in flare, £122, relatively high when tapering steroids, £30 to £40, and relatively low when off steroids, around £8. The shorter duration of tapering with upadacitinib helps reduce these costs.

The quality of life decrements of the various complications are drawn from the literature, mainly a reasonably standard set of values estimated from US data using the UK social tariff. The costs of GCA related complications are in large part drawn from the literature while those of steroid related and JAK related complications are in large part based on NHS reference costs.

The EAG has identified several errors in the company model. As summarised in greater detail in section 4.5.1 below, correcting these changes the company base case of upadacitinib being dominant, saving [REDACTED] with a net gain of [REDACTED] QALYs, to an ICER of £38,359 per QALY. The effects of the individual error are presented in **Table 42** The EAG corrects for previous steroid use by running the model for the new onset assuming no prior steroid use, and taking the [REDACTED] day steroid usage estimates and applying these to the relapsed subgroup. The resulting weighted averages provide the baseline values for the ITT population.

The results of correcting these errors are presented in Table 42. Since Error 02 and Error 06 can be viewed as being bound up together their joint effect is also presented.

The EAG corrected company base case ICER is considerably different from the uncorrected ICER so the EAG also presents the effects of disapplying the individual EAG corrections. Some changes, such as Error 01 that applies a mean baseline cumulative steroid dose, appear of minor importance when applied to the uncorrected company base case but are more important when disapplying to the EAG corrected company base case.

Table 42 of section 4.5.1 below. For reasons of space the EAG describes these errors alongside the detailed description of the model in this chapter.

1. Error 01: The cumulative steroid dose at baseline is not considered: Section 3.2.3.

2. Error 02: Only patients on steroids risk conditions that are exacerbated by steroid use despite the model assuming that risks are determined by the total prior steroid dose. Those not receiving steroids cannot develop conditions such as osteoporosis or diabetes: Section 3.2.6.8.
3. Error 03: The calculation of the incidence of permanent conditions does not consider their prevalences: Section 3.2.6.8.
4. Error 04: Annual incidences are converted to weekly probabilities assuming a survivor function rather than simply dividing the annual incidence by 52: 3.2.6.8.
5. Error 05: In the upadacitinib arm the upadacitinib 26-week steroid tapering schedule is retained after the 2-year stopping rule when the placebo 52 week tapering schedule should be applied: Section 3.2.6.9.
6. Error 06: The cumulative steroid dose calculation is not conditioned by the proportion surviving: Section 3.2.6.9.
7. Error 07: Prednisolone costs are a simple average rather than a market share weighted average: Section 3.2.9.2.

At clarification (B13), the company submitted a slightly revised model and revised base cases. These cost effectiveness estimates from these minor amendments are presented in section 4.2 for the ITT population. The EAG has not been able to replicate these results as the model changes were not documented.

The company submission presents results for the new onset and relapsed subgroups in appendices to its submission. The EAG presents these in this report. The EAG thinks that because TA518 approved tocilizumab for relapsed patients Committee may have to consider the subgroups separately. This inevitably leads to a rather lengthy presentation, though much of this is graphical.

Due to time constraints sections 3.2.1 through to 3.2.9 provide an account of the original company model rather than the lightly revised company model submitted at clarification.

3.2.3 Baseline cumulative steroid dose

The patient baseline characteristics are taken from the SELECT-GCA ITT population, as are the baseline steroid dose distributions differentiated by arm

Table 24: Baseline patient characteristics

Age	71.1 years	
Female	73%	
Cumulative steroid use	0 mg	
Baseline steroid daily use	Upadacitinib	Placebo
60mg	■	■
50mg	■	■
40mg	■	■
30mg	■	■
20mg	■	■

Error 01: The modelling of conditions exacerbated by steroid use is based upon the cumulative prior dose of steroids. This is assumed to be zero at baseline. This will not be the case for the relapsed who within SELECT had an average duration of diagnosis of around ■ days. The EAG approach is to model the new onset with a baseline cumulative dose of 0 mg, and estimate the relapsed baseline cumulative dose from the ■ day figure among the new onset. This yields a weighted average cumulative dose across the ITT population of 1,322mg.

Therkildsen et al⁶⁸ supply a mortality multiplier of 1.03 for GCA and also a mortality multiplier for when in flare and during the year after flare of 1.49

Given the high baseline age, the proportion surviving drops away reasonably quickly. The company base case estimates only muted survival gains of a little over 4 weeks from upadacitinib.

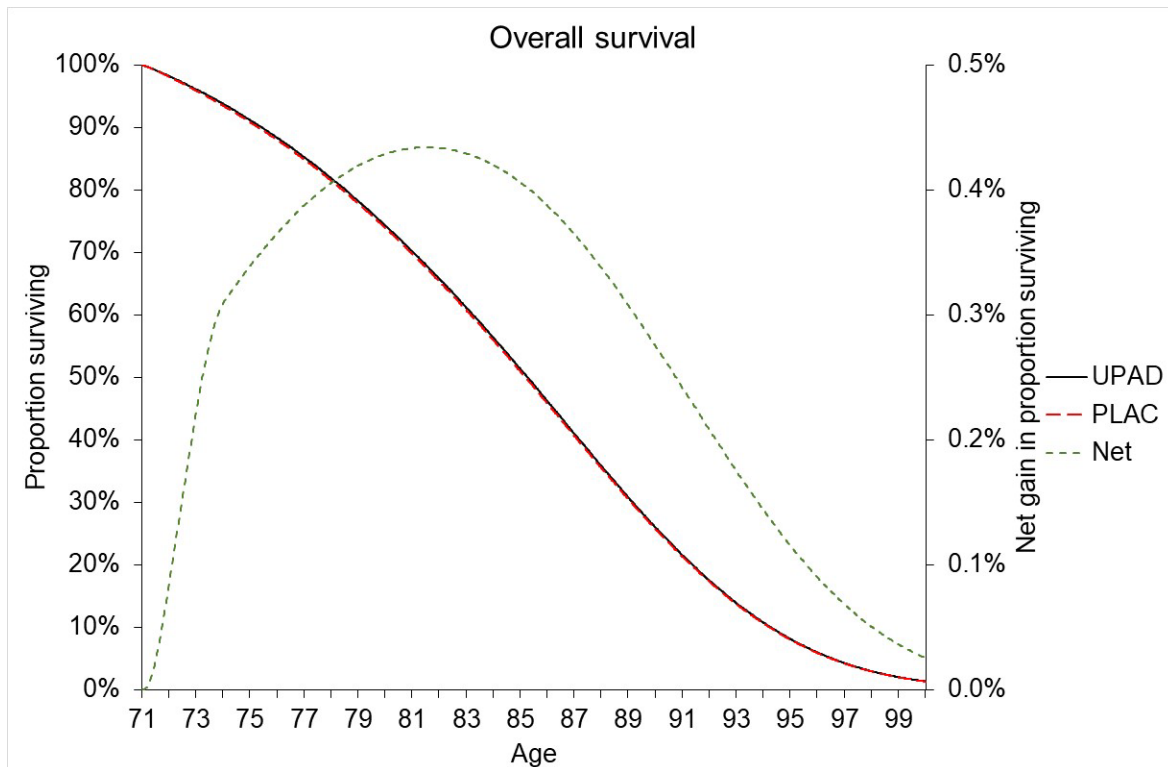


Figure 33: Company base case overall survival: ITT population

Figure 42 presents overall survival for the ITT modelling. The overall survivals for the new onset subgroup and the relapsed subgroup are very similar. For reasons that are unclear the company uses 2018-2020 life tables rather than 2021-23 life tables, but this has minimal effect

3.2.4 Interventions and comparators

The company base case compares

- Upadacitinib, a 26-week steroid taper and a 2 year stopping rule, with
- Placebo and a 52-week steroid taper.

Tocilizumab is a comparator in the scope. The company does not consider tocilizumab in the economics due to it:

- Having a 1 year stopping rule,
- Only being approved for relapsed patients,

- The 1 year stopping rule leading to access challenges and limiting its use, and
- A requirement for Blueteq authorisation.

Given the proposed 2 year stopping rule for upadacitinib the relevance of the 1 year stopping rule for tocilizumab when assessing whether it should be a comparator is unclear.

The EAG does not know if Blueteq authorisation will be required for upadacitinib if it is approved. The costs of a 2 year course of upadacitinib and a 1 year course of tocilizumab are provided in the confidential cPAS appendix.

3.2.5 Perspective, time horizon and discounting

These are aligned with the NICE reference case.

3.2.6 Treatment effectiveness and extrapolation

3.2.6.1 Time to first flare (TTFF): ITT population

The company fits the standard set of curves to SELECT-GCA Period 1 Kaplan Meier (KM) data. These are shown alongside the Kaplan Meier curves in Figure 43 and Figure 44 below. The Kaplan Meier curve for proportion not having flared is labelled KM S(t) and read off the left vertical axis while the Kaplan Meier number at risk is labelled KM N and read off the right vertical axis.

The company censors those not in remission at baseline due to the Committee concerns about this in TA518, ■ out of 209 in the upadacitinib arm and ■ out of 112 in the placebo arm. This is the reason for the drop in the numbers at risk at Day 0. Note that all Kaplan Meier data is taken from the company clarification response as this provides numbers at risk. This differs from the summary Kaplan Meier data that was included in the original electronic model.

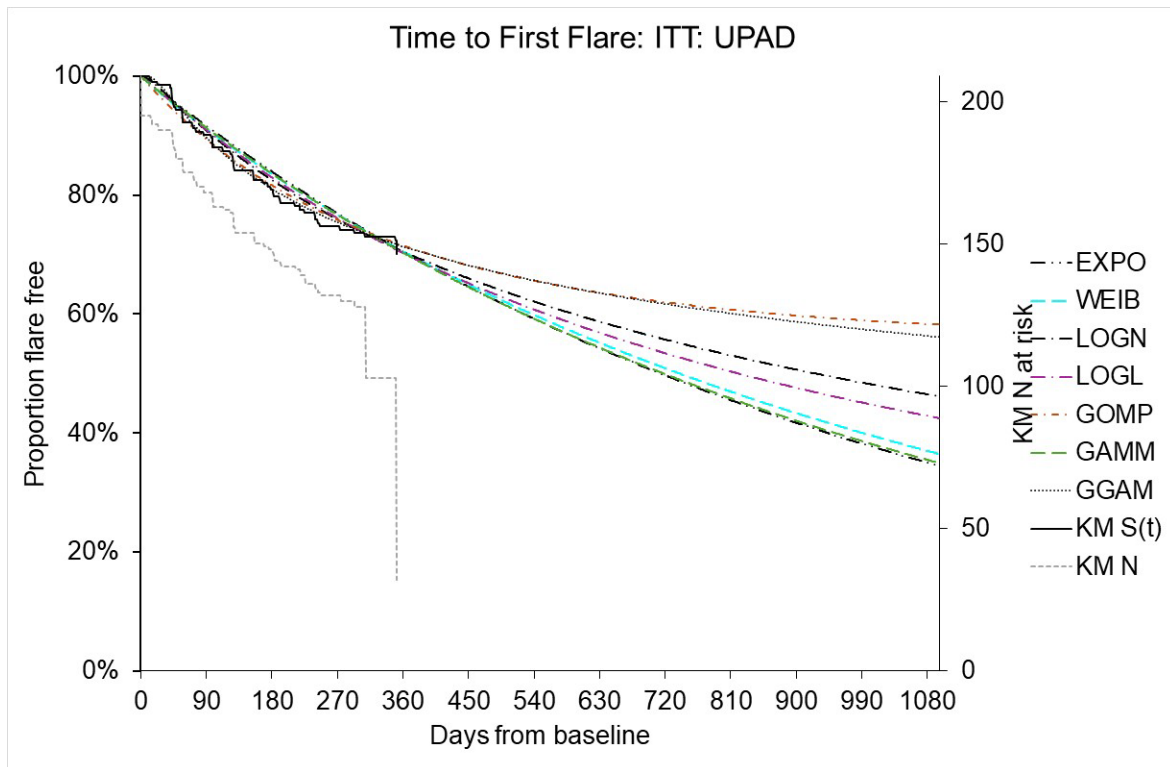


Figure 34: Company TTFF curves: Upadacitinib: ITT

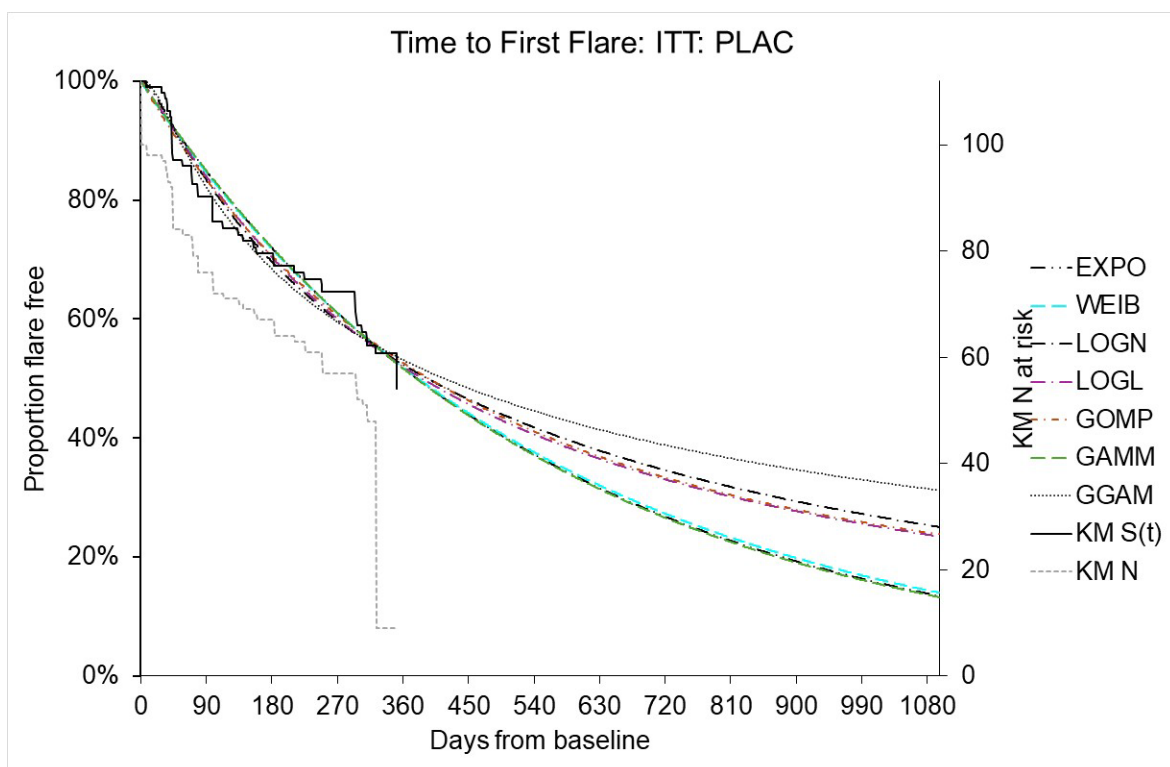


Figure 35: Company TTFF curves: Placebo: ITT

The information criteria are presented in Table 25: AIC: Akaike Information Criterion and BIC: Bayesian Information Criterion. The company notes that the generalised gamma has the best AIC in the upadacitinib arm with the log-normal providing a comparable fit, though it does not comment upon the BIC where the lognormal has the lowest value. Likewise, for the placebo arm the company concentrates upon the AIC and notes that the log-normal has the best fit.

The company submission states it further validated extrapolations through expert opinion, reporting that this supported the log-normal extrapolations. At clarification the company supplied the report of the expert advisory board. The report presents results for the new onset subgroup and the expert opinion around this. The EAG can find no reference to the ITT population curves within the advisory board report. The company could at error check provide the detail of the clinical consultation referred to in the second last paragraph of Page 120 of its submission.

Table 25: ITT: Time to first flare curves' information criteria

Upadacitinib	EXPO	WEIB	LOGN	LOGL	GOMP	GAMM	GGAM
AIC	624.4	626.3	620.8	624.6	623.6	626.4	619.4
BIC	627.8	633.0	627.5	631.3	630.3	633.1	629.4
Placebo	EXPO	WEIB	LOGN	LOGL	GOMP	GAMM	GGAM
AIC	473.6	475.6	472.1	474.5	475.2	475.6	473.3
BIC	476.4	481.1	477.5	479.9	480.7	481.1	481.4
EXPO: Exponential, WEIB: Weibull, LOGN: Log-normal, LOGL: Log-logistic, GOMP: Gompertz, GAMM: Gamma, GGAM: Generalized gamma							

In the upadacitinib arm the upadacitinib curve's probabilities of flare are applied for the first 2 years. After this, due to the 2 year stopping rule the contemporaneous placebo probabilities of flare are applied. This results in the proportions modelled as surviving and as flare free of Figure 45.

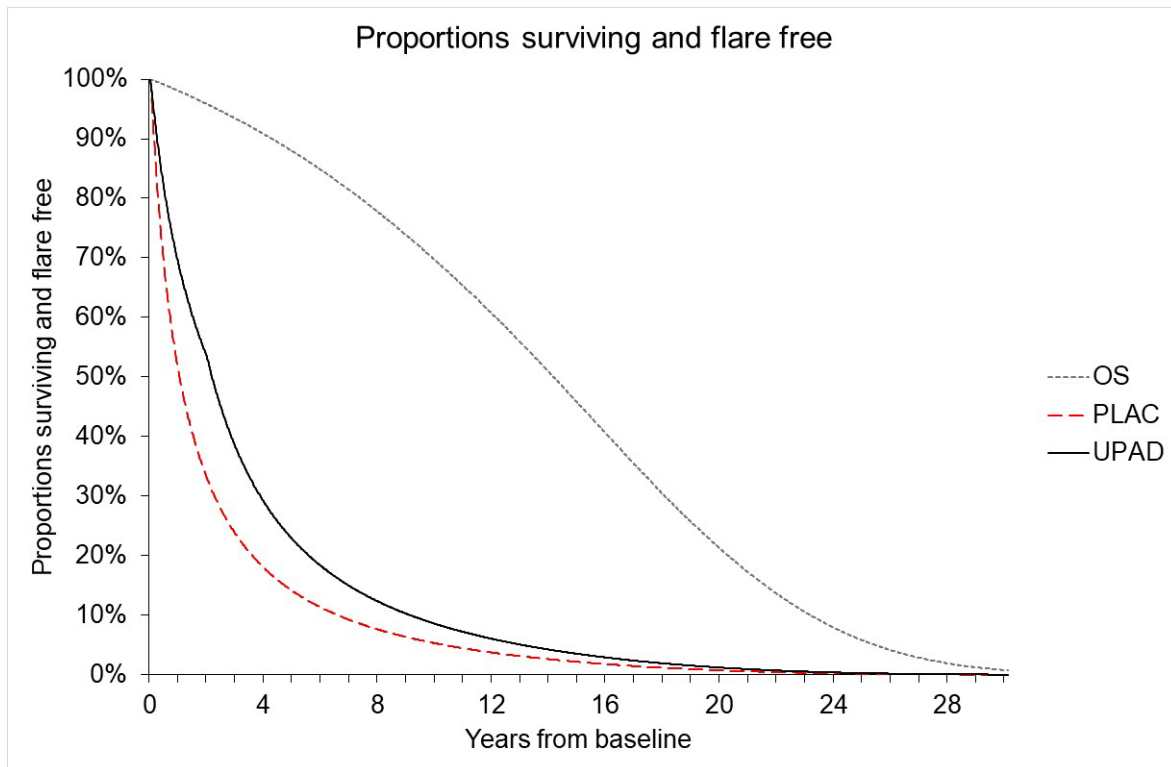


Figure 36: ITT: Proportions surviving and proportions flare free

The proportion of those who are alive and flare free is presented in Figure 46, as this provides a better indication of the application of the TTFF curves within the modelling.

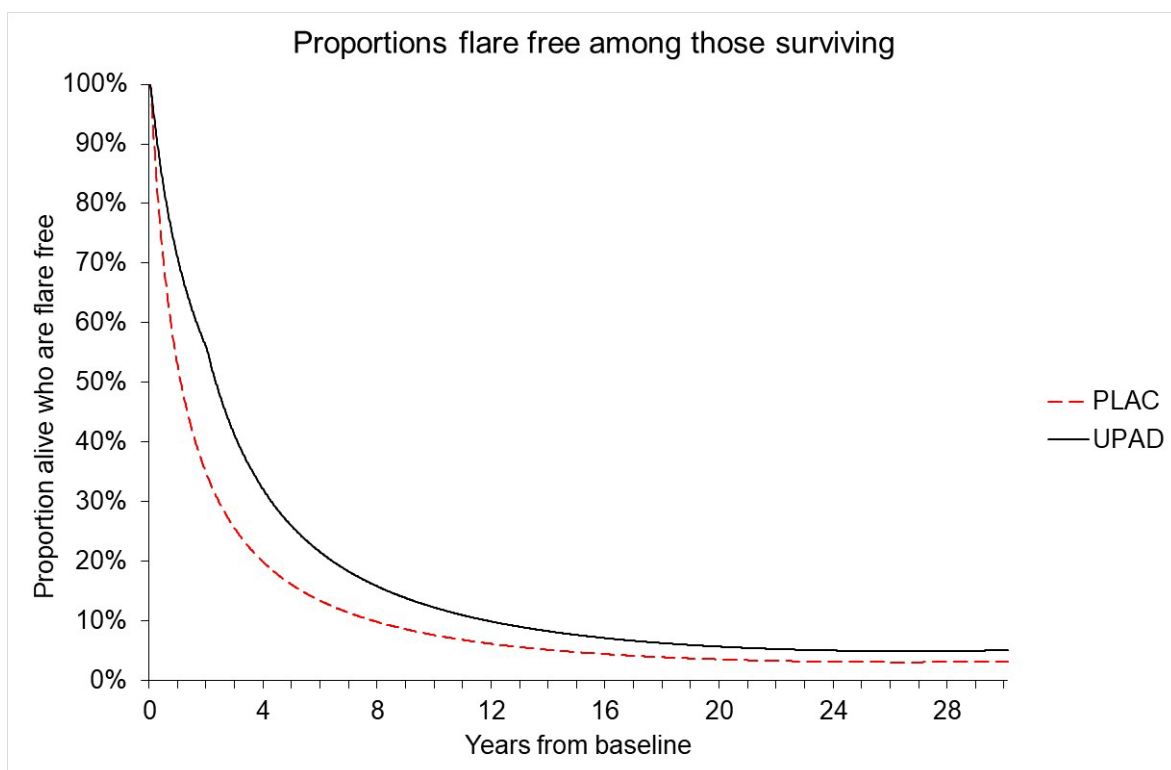


Figure 37: ITT: Proportions of those surviving who are flare free

3.2.6.2 Time to subsequent flare (TTSF): ITT population

The company estimates weekly risks of subsequent flares from SELECT-GCA Period 1 data using a Poisson regression: 0.69% for those receiving upadacitinib and 1.13% for those receiving placebo. The EAG assumes that these weekly risks can be annualised using the standard formula of $1 - (1 - P)^{(7 / 365.25)}$ given the company approach elsewhere, yielding estimates of 30% and 45% respectively¹. This does not take into account that those who have a subsequent flare will after 4 weeks have the same 0.69% and 1.13% weekly risks of flaring again. Allowing for this yields an annual incidence of subsequent flares among those who have previously flared of 35% for upadacitinib and 57% for placebo. These coincide with the initial annual probabilities of first flare as shown in Figure 47 below.

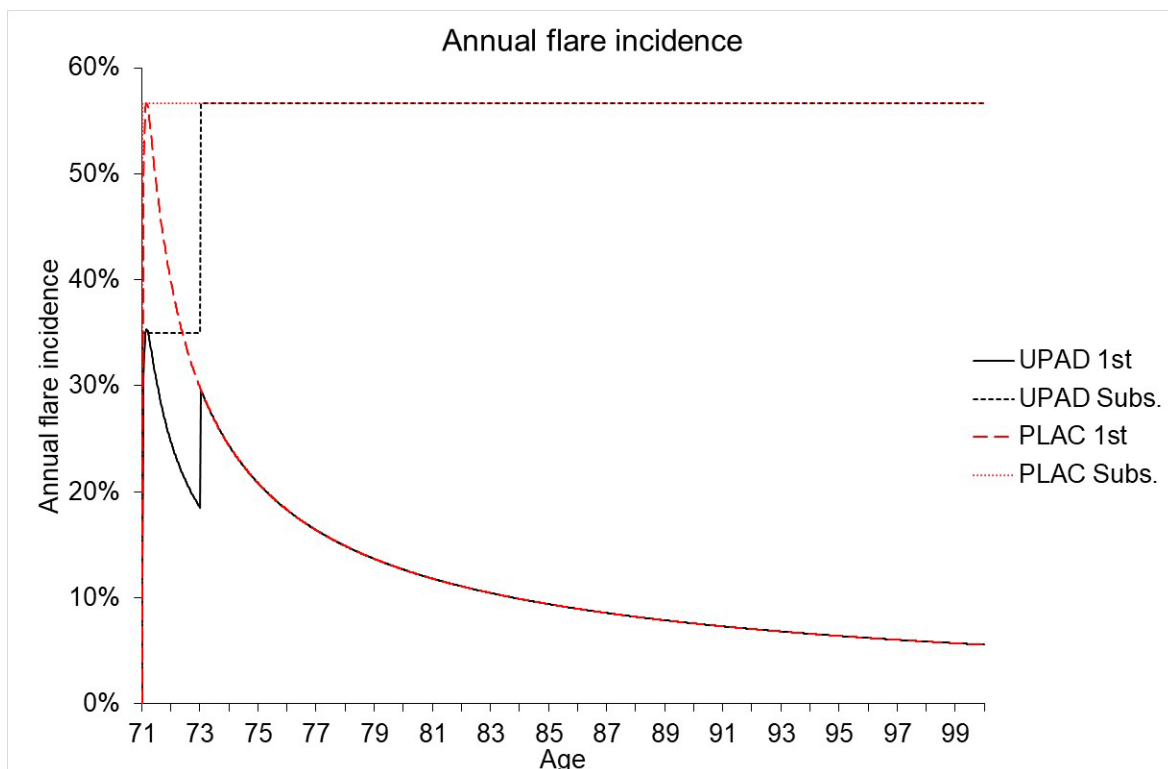


Figure 38: ITT Annualised flare incidences

¹ See worksheet *EAG Graph Data* cells AN5:AR64.

Figure 47 illustrates the annual incidences of flares, with the upadacitinib arm probabilities joining those of the placebo arm from year 2 onwards. The lower probabilities of first flare in the upadacitinib arm up to year 2 causes fewer to have had a first flare by year 2. This results in an ongoing benefit as these patients experience the lower probabilities of first flare from year 2 rather than the somewhat higher 57% annual incidence of subsequent flares.

3.2.6.3 Time to first flare (TTFF): New Onset subgroup

The standard set of curves fitted to SELECT-GCA Kaplan Meier data for the new onset subgroup is presented in [REDACTED] and [REDACTED], [REDACTED] out of 148 in the upadacitinib arm and [REDACTED] out of 76 in the placebo arm being censored for not being in remission at baseline.

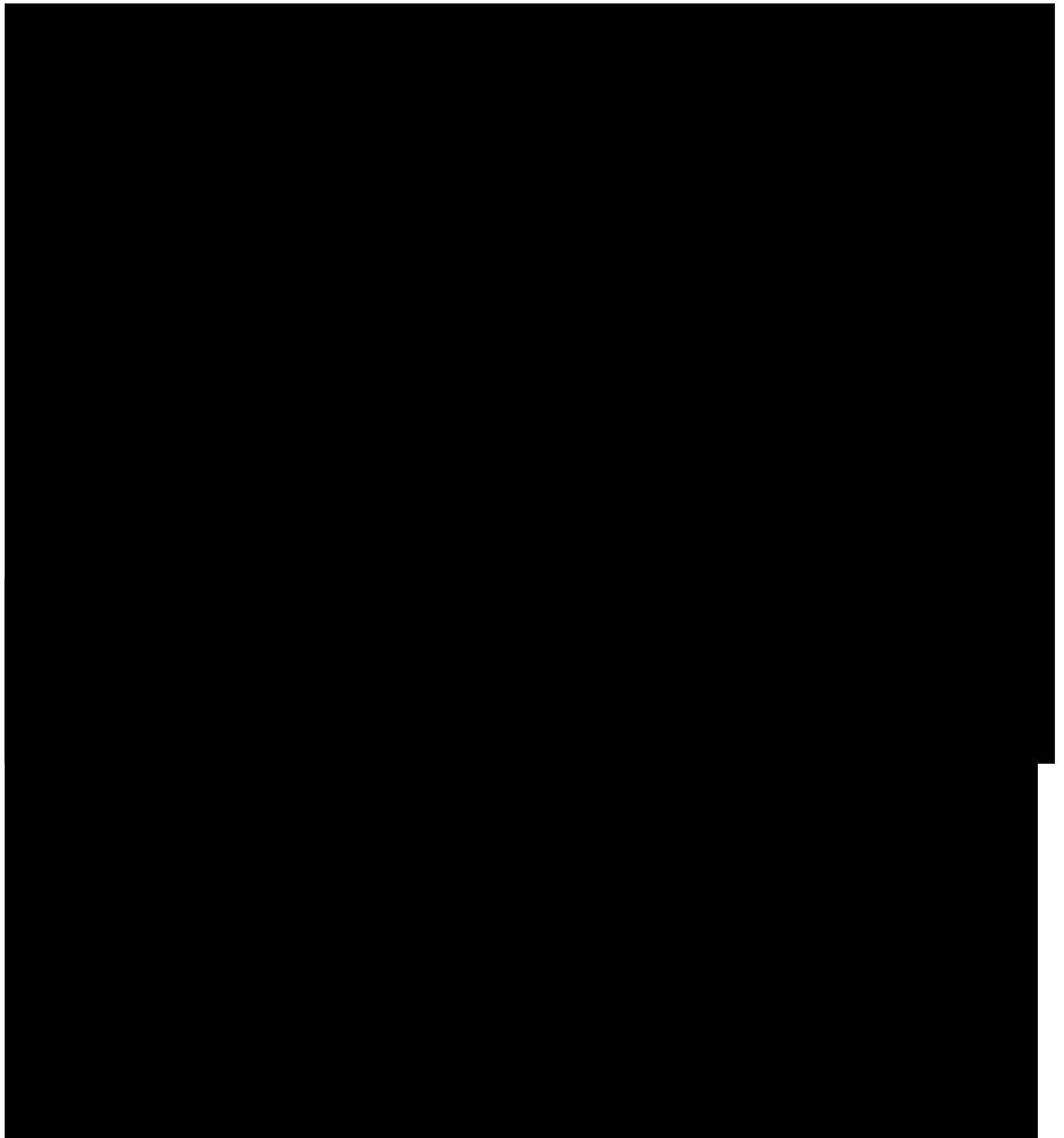


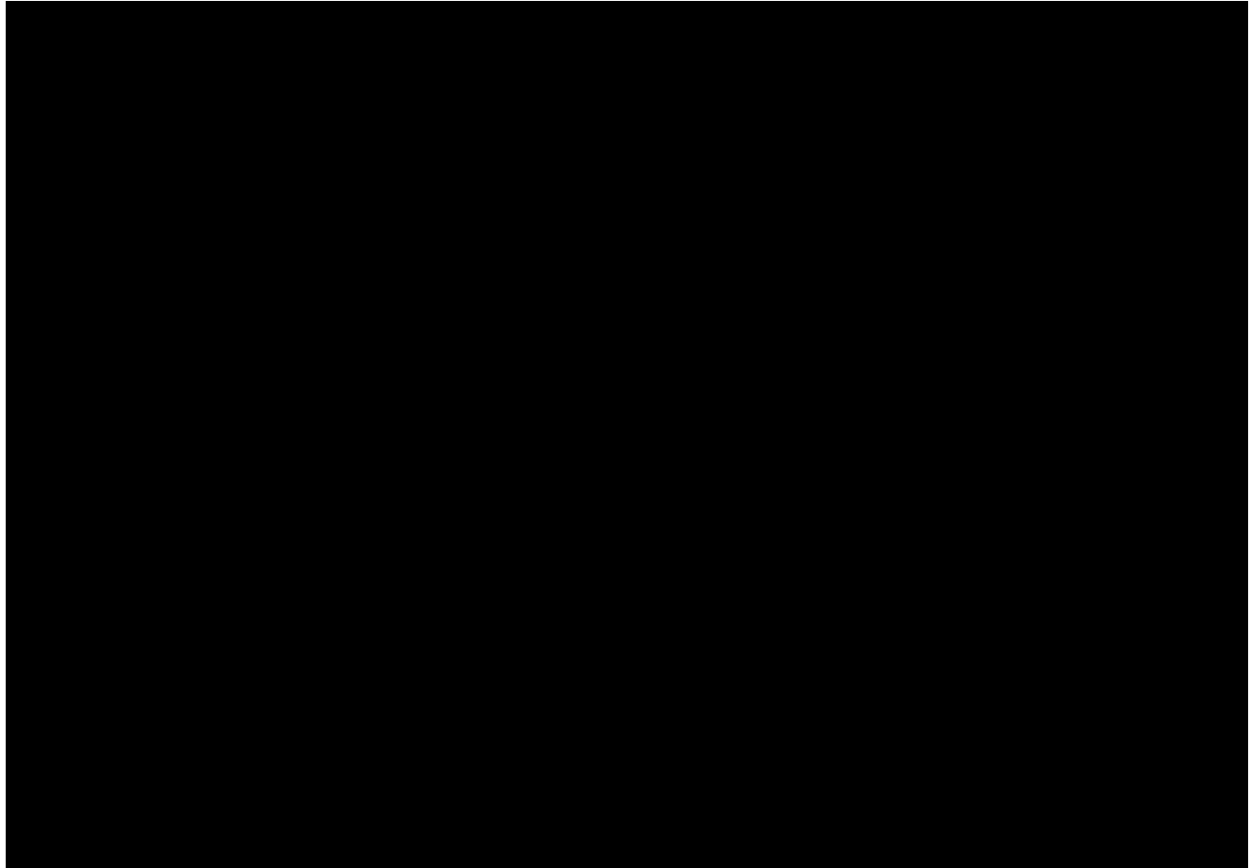
Table 26: New Onset subgroup: Time to first flare curves' information criteria

Upadacitinib	EXPO	WEIB	LOGN	LOGL	GOMP	GAMM	GGAM
AIC	425.4	426.4	422.3	425.3	423.0	426.7	420.6
BIC	428.4	432.4	428.3	431.3	429.0	432.7	429.6
Placebo	EXPO	WEIB	LOGN	LOGL	GOMP	GAMM	GGAM
AIC	311.5	313.0	309.3	311.4	311.1	313.2	309.7
BIC	313.8	317.7	314.0	316.0	315.7	317.9	316.7
EXPO: Exponential, WEIB: Weibull, LOGN: Log-normal, LOGL: Log-logistic, GOMP: Gompertz, GAMM: Gamma, GGAM: Generalized gamma							

The information criteria are presented in Table 26. The company chooses the Gompertz on the basis of the information criteria and its expert advisory board.

As shown in [REDACTED] and [REDACTED] by year 3 both Gompertz curves exceed the other curves, but more importantly they have both largely plateaued. This means that from

year 3 there is little to no probability of flares among those who have not flared, which in turn means that the absolute gain from upadacitinib use is retained indefinitely. This results in the proportions modelled as surviving and as surviving and flare free of [REDACTED].



41

The proportion of those who are alive and flare free is presented in [REDACTED], as this provides a better indication of the application of the TTFF curves within the modelling.



42

illustrates how the choice of the Gompertz results in the absolute gain from upadacitinib use being maintained indefinitely after three years because the Gompertz curves have little to no probability of first flare from year 3. The proportion who are flare free increases due to the higher mortality among those who have subsequently flared. The net gain from upadacitinib is a permanent or so gain in the proportion who never flare. This also translates into an ongoing cumulative steroid sparing effect because around fewer patient in the upadacitinib arm are subject to the annual incidence of subsequent flares, as presented in section 3.2.6.4 below.

3.2.6.4 Time to subsequent flare (TTSF): New Onset subgroup

The company estimates weekly risks of subsequent flares from SELECT-GCA Period 1 data using a Poisson regression: for those receiving upadacitinib and

████ for those receiving placebo. The EAG converts these to annual incidences of █████ and █████. This results in the annualised incidences of █████

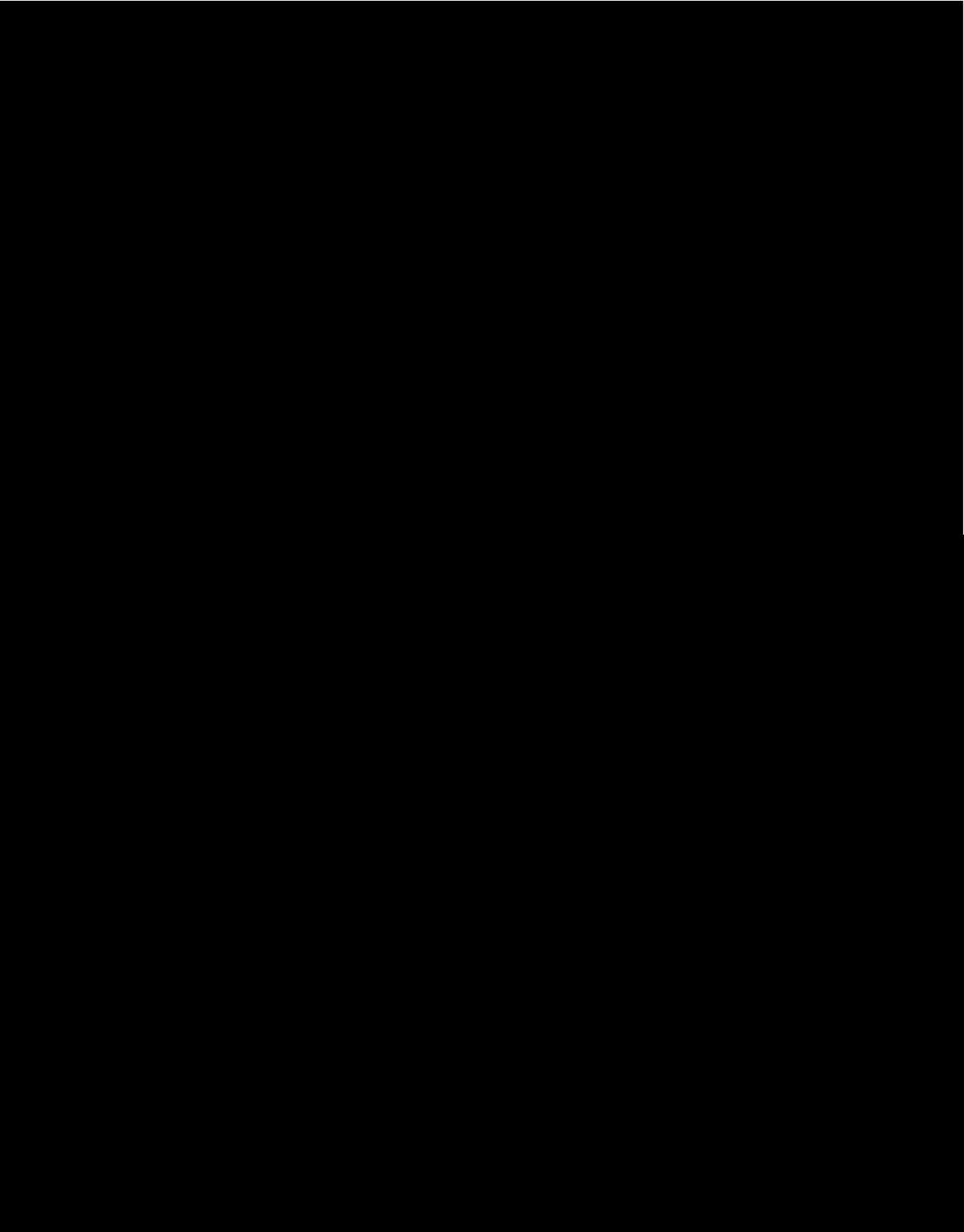
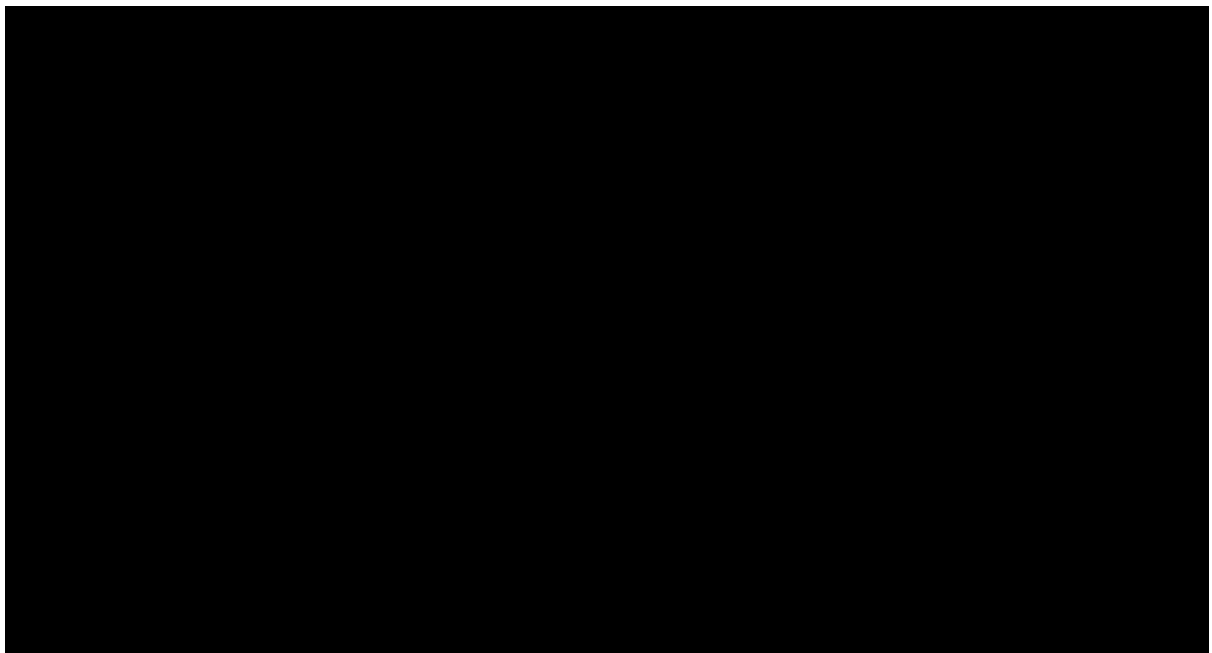


Table 27: Relapsed subgroup: Time to first flare curves' information criteria

Upadacitinib	EXPO	WEIB	LOGN	LOGL	GOMP	GAMM	GGAM
AIC	200.5	201.6	199.6	200.9	202.5	201.4	200.0
BIC	202.6	205.9	203.8	205.1	206.7	205.6	206.4
Placebo	EXPO	WEIB	LOGN	LOGL	GOMP	GAMM	GGAM
AIC	164.1	165.2	165.5	165.7	164.9	165.3	166.7
BIC	165.7	168.4	168.6	168.9	168.1	168.4	171.4
EXPO: Exponential, WEIB: Weibull, LOGN: Log-normal, LOGL: Log-logistic, GOMP: Gompertz, GAMM: Gamma, GGAM: Generalized gamma							

The information criteria are presented in Table 27. The company chooses the log-normal curves principally on the basis of the information criteria. This results in the proportions modelled as surviving and as flare free of [REDACTED].

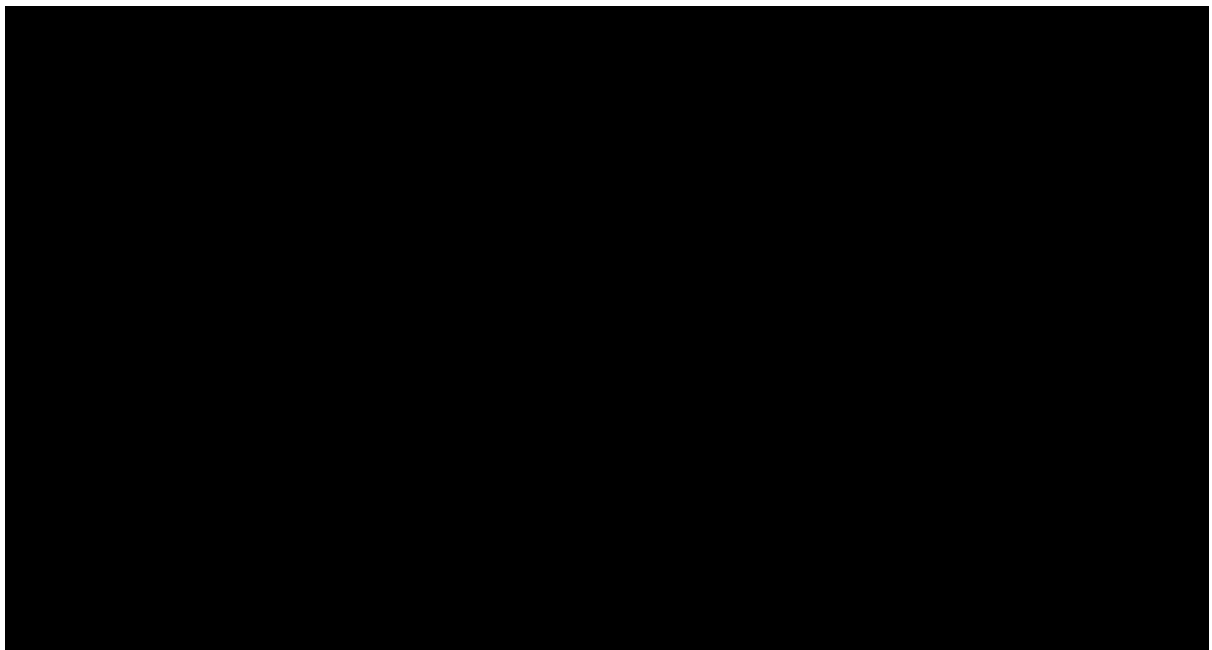
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46

As before, the proportion of those who are alive and flare free is presented in [REDACTED] as this provides a better indication of the application of the TTFF curves within the modelling.

47



The gain from upadacitinib in the proportion of those surviving who remain flare free for the relapsed subgroup is modelled as very much less than that for the new onset population.

3.2.6.6 Time to subsequent flare (TTSF): Relapsed subgroup

The company estimates weekly risks of subsequent flares from SELECT-GCA Period 1 data using a Poisson regression: [REDACTED] for those receiving upadacitinib and [REDACTED] for those receiving placebo. The EAG converts these to annual incidences of [REDACTED] and [REDACTED]. The estimate for upadacitinib is considerably less than that for the ITT population. This results in the annualised incidences of first flare and subsequent flare of [REDACTED].



3.2.6.7 Conditions related to GCA flares

Annual probabilities are presented in Table 28. The model converts these to weekly probabilities and applies them to those in flare. Total costs per incident event are applied together with an annual quality of life decrement.

Nuenninghoff et al⁶⁹ estimated 18.7 aortic aneurisms and/or dissection per 1,000 patient years among 168 patients identified with GCA in Olmsted County, Minnesota

between 1950 and 1999, or an annual probability of 1.87%, which the company splits 60:40 between aortic aneurism and aortic dissection.

Yates et al⁷⁰ estimated probabilities of unilateral and bilateral vision loss of 7.85% and 1.38% during the 6 months following GCA diagnosis among 433 patients with GCA across 26 countries.

Amiri et al⁷¹ estimated 38.1 myocardial infarctions per 1,000 patient years among all 809 patients with GCA between 1996 and 2010 in British Columbia.

Gonzalez-Gay et al⁷² report 8 strokes among 287 patients between onset of GCA symptoms and 4 weeks after the onset of corticosteroid use. The company assumes a 4 week period, annualising this to a probability of stroke of 36.2% resulting in 3% of patients who flare having a stroke during their flare period. The company splits this 40:60 between major stroke and minor stroke.

Aortic aneurism and aortic dissection are assumed transient, their quality of life impact lasting one year so in effect being a QALY decrement.

Vision loss, having had a previous MI, major stroke and minor stroke are assumed permanent with an ongoing annual quality of life decrement but no further costs due to these being within the total incident costs.

Quality of life values are largely taken from the standard catalogue of values of Sullivan et al,⁷³ the values for vision loss being taken from Konig et al.⁷⁴

Stroke costs are five year costs. The cost for bilateral blindness is a discounted roughly ten year cost, based upon the estimated mean survival in the upadacitinib arm.

It is assumed that for those not in flare their risks of the conditions are zero.

Table 28: GCA flare related conditions' probabilities, cost and quality of life

	Annual Prob.	4 Wk Prob.	Incident cost	QoL
Aortic aneurism	1.12%	1.25%	£12,688	-0.054
Aortic dissection	0.75%	0.11%	£27,642	-0.129
Vision loss - unilateral	15.09%	0.09%	£7,258	-0.040
Vision loss - bilateral	1.38%	0.06%	£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

3.2.6.8 Conditions related to cumulative steroid dose: Errors 02, 03, 04

The company analyses a US insurance database, identifying patients newly diagnosed with GCA and with up to 5 years of follow up data and at least 1 year follow up data since either GCA diagnosis or steroid initiation up to 3 months prior to GCA diagnosis.

To be included patients were also required to not have claimed for steroid use in the 12 month to 3 month period prior to GCA diagnosis, to have claimed for steroid use thereafter and have received at least 30 days but no more than 360 days supply after GCA diagnosis. This may be since initiation of steroid use, the paper is ambiguous.

An unpublished paper is presented, alongside an additional undocumented analysis by the company which appears to be bespoke for the current submission. These differ in the boundaries between risk categories, the company analysis splitting this into 5 risk categories based upon the mean daily steroid dose in the year since GCA diagnosis, or rather the year since GCA diagnosis plus any steroid use up to 90 days prior to GCA diagnosis:

1. Low risk: less than 5mg 
2. Medium risk: between 5mg and 10mg 
3. High risk: between 10mg and 20mg 
4. Very high risk: between 20mg and 40mg 
5. Extremely high risk: greater than 40mg 

New diagnoses of conditions possibly exacerbated by steroid use within the first year since GCA diagnosis are identified for each of the above five groups. Having had a previous diagnosis of one condition bars a patient from contributing to estimates for that condition, but not for others.

In the following the EAG assumes that the methods of the company bespoke analysis are the same as those presented in the unpublished paper.

Most conditions affected by steroid use are assumed to be transient. The quality of life decrement is assumed to last one year so is equal to the QALY decrement.

Costs are in large part taken from NHS reference costs, with the more important of these being reviewed in section 5.4.2. Quality of life values are mostly taken from a reasonably standard set of values estimated for the UK from US EQ-5D data by Sullivan et al.⁷³

Table 29: Steroid related conditions that last one year, annual probability, cost and QALY

Risk group	Low	Med.	High	V.High	E.High		
N						Cost	QALY
Abnorm. Electrol						£1,764	-0.030
Palpitations						£1,334	-0.038
Non-traum fract.						£1,769	-0.068
GI perforation						£6,195	-0.068
Ulcer/GI bleed						£1,894	-0.057
Gastritis						£1,904	-0.044
Mental health						£2,869	-0.090
Infections						£2,282	-0.101
Sepsis						£3,377	-0.200
Severe infection						£4,263	-0.156
Cataract						£1,267	-0.033
Sleep disorders						£970	-0.037
Dyspnoea						£1,667	-0.050
Bruising						..	-0.003
Skin thinning						..	-0.003
Slowwound heal						..	-0.003
Acne						..	-0.065
Hirsutism						..	-0.045
Increased BMI						..	-0.004
Pre-diabetes						£61	-0.034
Type 2 diabetes						£1,680	-0.038
Hyperlipidaemia						..	0.000
Endoc. ad. ins.						£2,398	-0.030
Cushing's synd.						£1,099	-0.030

Myopathy	■	■	■	■	■	£1,004	-0.050
Asep. bone nec.	■	■	■	■	■	£45	-0.001
Hypertension	■	■	■	■	■	£759	-0.046
Abnorm. Electrol: Abnormal electrolytes, Non-traum. frac: Non-traumatic fracture, Endoc. ad. ins.: Endocrine adrenal insufficiency. Asep. bone nec.: Aseptic bone necrosis. * Severe infections are Hospitalisations with infection as primary discharge code.							

Other conditions once acquired are ongoing and have ongoing annual costs and quality of life effects, Table 30 presenting these. The main steroid gradients are for atherosclerosis, osteoporosis and glaucoma.

Table 30: 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	■	■	■	■	■	Ann.Cost	QoL
Heart failure*	■	■	■	■	■	£2,772	-0.117
Tendon rupture	■	■	■	■	■	£1,342	-0.150
Hyperlipidaemia	■	■	■	■	■	£18	-0.007
Bone necrosis	■	■	■	■	■	£2,335	-0.060
Atherosclerosis	■	■	■	■	■	£1,157	-0.036
Osteoporosis	■	■	■	■	■	£76	-0.042
Glaucoma	■	■	■	■	■	£827	-0.039
* Note that heart failure is hospitalisation for heart failure							

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

1. Low risk: less than 1,826mg
2. Medium risk: between 1,826mg and 3,653mg
3. High risk: between 3,653mg and 7,305mg
4. Very high risk: between 7,305mg and 14,610mg
5. Extremely high risk: greater than 14,610mg

Within the US insurance dataset these values map the new diagnoses of conditions in the year since diagnosis, or rather in the period since initiation of steroids which could be 90 days prior to GCA diagnosis, against the cumulative dose in the year since diagnosis. The key assumptions when modelling the incidences of steroid related conditions are:

- The steroid gradient relationships during the first year since GCA diagnosis hold for all subsequent years.
- The steroid gradient relationships hold for the total cumulative steroid dose since diagnosis; i.e. a patient on an average ongoing steroid dose of 4mg has a cumulative steroid dose after 1 year of 1,461mg so is low risk, after 2 years a cumulative dose of 2,922mg so is medium risk, after 3 years a cumulative dose of 4,383mg so is high risk, and so on.
- There are no confounding variables.

The above account slightly simplifies things. The model is a Markov model which tracks the mean cumulative dose across the cohort. It is the mean cumulative steroid dose across the cohort that is compared to the risk boundaries outlined above.

Error 02: It is assumed that despite the risk of events being based upon the previous cumulative steroid dose only those on steroids in any given cycle are at risk of steroid related conditions. Those not on steroids during that cycle are assumed to have zero risk of conditions the risks of which are exacerbated by steroid use. This also needs to be read alongside the quite high incidences of some conditions even among the low risk group, and as reviewed in more detail in section 5.2.7 below.

Error 03: The incidence of complications that are permanent does not take into account the prevalences of these complications, so overestimates their incidences. For instance, the company base case estimates that in the placebo arm after 6.6 years when 83% of patients remain alive 100% will have osteoporosis. This continues to increase thereafter to 170% of those alive at 10 years and 285% of those alive at 15 years.

Error 04: The company converts annual incidences of conditions such as dyspnoea into weekly probabilities using the standard $1 - (1 - P)^{(7 / 365.25)}$ formula. This is correct for a survival analysis where patients can experience the event only once with the eligible population being progressively reduced by the weekly incidences of

events. The model does not reduce the eligible population by the weekly incidences of events so the total incidence of events over the year is overestimated.

This is unlikely to affect results where the annual incidence is small. An annual incidence of 10.0% is modelled as 10.5% using this method. But this is non-trivial for conditions with higher incidences and reasonable effects upon model outputs in terms of net costs and/or net QALYs. A 20.0% annual incidence is modelled as 22.2%, 30.0% as 35.3% and 40.0% as 50.3%.

3.2.6.9 Cumulative steroid dose: Errors 05, 06

The cumulative steroid dose is the sum since baseline of the daily steroid use. This is not conditioned by the proportion remaining alive or by the proportion remaining alive and receiving steroids. The company base case results in the following mean daily steroid dose.

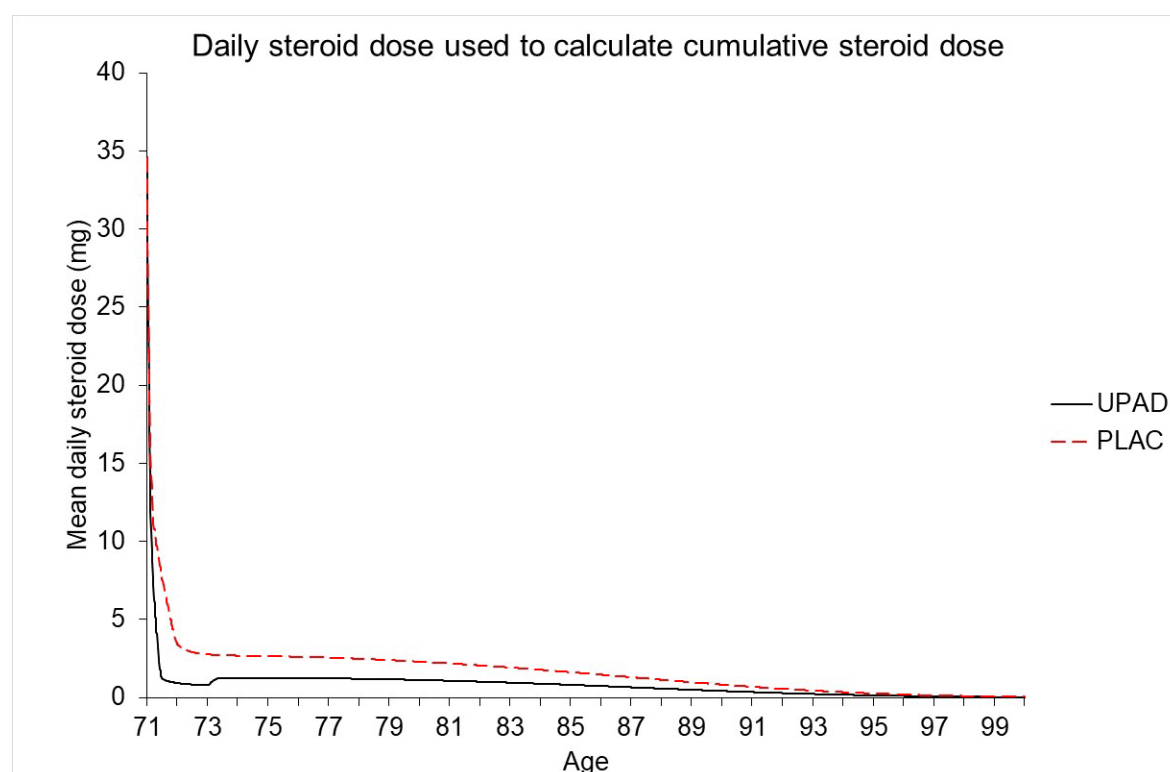


Figure 49: Company base case mean daily steroid dose

The daily steroid dose falls away quite quickly and continues to decline thereafter.

Error 05: The gap between upadacitinib and placebo after upadacitinib treatment is stopped at 2 years is mainly due to the model retaining the upadacitinib 26 week tapering schedule in the upadacitinib arm. If the placebo 52 week tapering schedule is applied the upadacitinib curve largely coincides with the placebo curve from 2½ years. Note that during FAC the company disputes that this is an error but is rather an assumption. The EAG maintains that modelling patients who stop upadacitinib treatment at 2 years and flare at, say, 4 years as then following the 26 week upadacitinib steroid tapering schedule is an error.

Error 06: The daily steroid dose tails off as patients age. This is due to the daily steroid dose not being conditioned by survival. An illustrative example is presented in Table 31 below for four cycles where the proportions surviving are 100%, 50%, 30% and 10%. In each cycle half of those alive are not on steroids, the other half being on a steroid dose of 40mg. This results in a mean dose of 20mg each cycle, and a total mean dose per surviving patient at the end of the fourth cycle of 80mg. The company method estimates a mean dose in, say, the 4th cycle of 5% * 40mg = 2mg. This results in a final total mean dose of 36mg².

Table 31: Calculation of daily steroid dose to be added to cumulative total

			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

In the fourth cycle the company method in effect says 5% had a dose of 40 mg because they were on steroids, 5% had a dose of 0 mg because they were off steroids, and 90% of patients had a dose of 0 mg because they had died: therefore, the relevant mean dose is 2 mg. Adding a mean of only 2 mg to the cumulative total in the 4th cycle is incorrect and is why the mean daily steroid dose continues to decline in Figure 58. Correcting this causes the mean daily steroid dose to plateau

² Note that the company calculation is correct for calculating the total costs of the steroids used. It is incorrect for calculating the total steroid exposure among those surviving.

from the 2½ year point as might be expected given the constant annual risk of subsequent flare.

During FAC the company raised an issue around this and steroid use being conditioned by survival, but raised no issues around Table 31. To avoid any ambiguity suppose that a cohort of 1,000 patients was simulated and after time only 1 patient survived. Further assume that this sole survivor is on a daily steroid dose of 20mg. When calculating the additional daily steroid dose that is relevant to this patient for assessing his/her risks from steroid use the company method estimates an additional dose of 0.02 mg. The EAG correction estimates an additional dose of 20mg.

There may be a debate about whether the steroid dose should be conditioned by the proportion on steroids and so increased by 40mg each cycle to yield a mean cumulative dose of 160mg, or by the proportion alive and so increased by 20mg to yield a mean cumulative dose of 80mg. The EAG thinks the former is incoherent as it is not obvious that the 40mg that relates to the 15% currently on steroids can simply be added to the running total that includes previous periods' dosing which will relate to other patients.

The above also needs to be read alongside the company assumption that only those on steroids in any given week are at risk of conditions exacerbated by steroid use. It should also be noted that the company market survey data relates to the year immediately following GCA diagnosis with patients having been required to have had at least 30 days steroid use. But it does not seem reasonable to assume that only those receiving steroids can develop T2DM, or osteoporosis or the like. The EAG also thinks that it would be incoherent for the risk of a condition for those on steroids to be a function of their total cumulative steroid dose to date but for this risk to fall to zero once tapering has been completed despite their total cumulative steroid dose to date, as summarised in section 3.2.6.8 above. If the total cumulative steroid dose to date determines the risk it is difficult to see why this risk should fall to zero. There may be an argument for modelling some conditions risks as being based upon the previous year's cumulative steroid dose as reviewed in section 5.2.6 but this is a separate argument.

The EAG thinks that the cumulative steroid dose should be that which applies to the surviving cohort, and that all these patients are at risk of the conditions the risks of which are exacerbated by steroid use.

The company base case results in mean cumulative steroid doses of Figure 59. This is augmented by the cut-offs for medium risk, high risk, very high risk and extremely high risk.

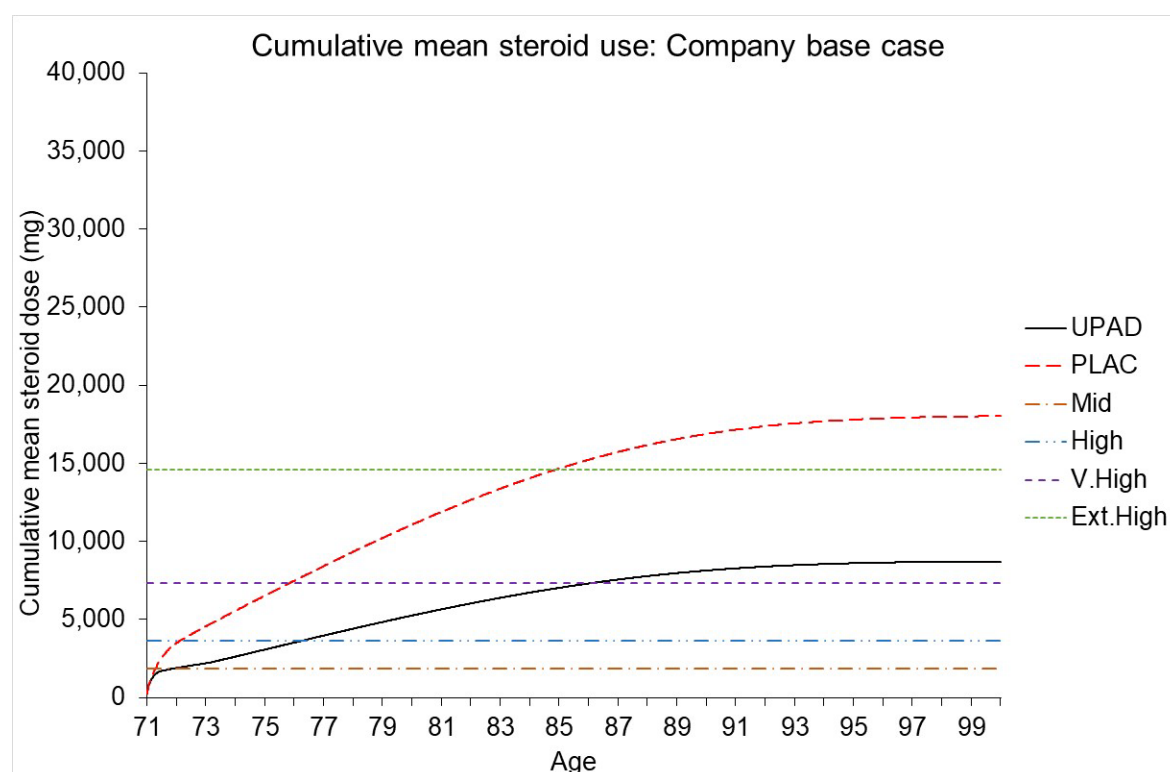


Figure 50: Company ITT base case cumulative steroid dose per surviving patient

The company base case suggests that patients in the upadacitinib arm only cross into being at very risk when age 86 years, 10 years later than in the placebo arm. Patients in the upadacitinib arm never cross into being at extremely high risk, while those in the placebo arm do so when age 85 years.

The increasing separation between the two curves is due to the retention of the upadacitinib 26 week tapering schedule after cessation of upadacitinib treatment. Correcting this aspect results in Figure 60

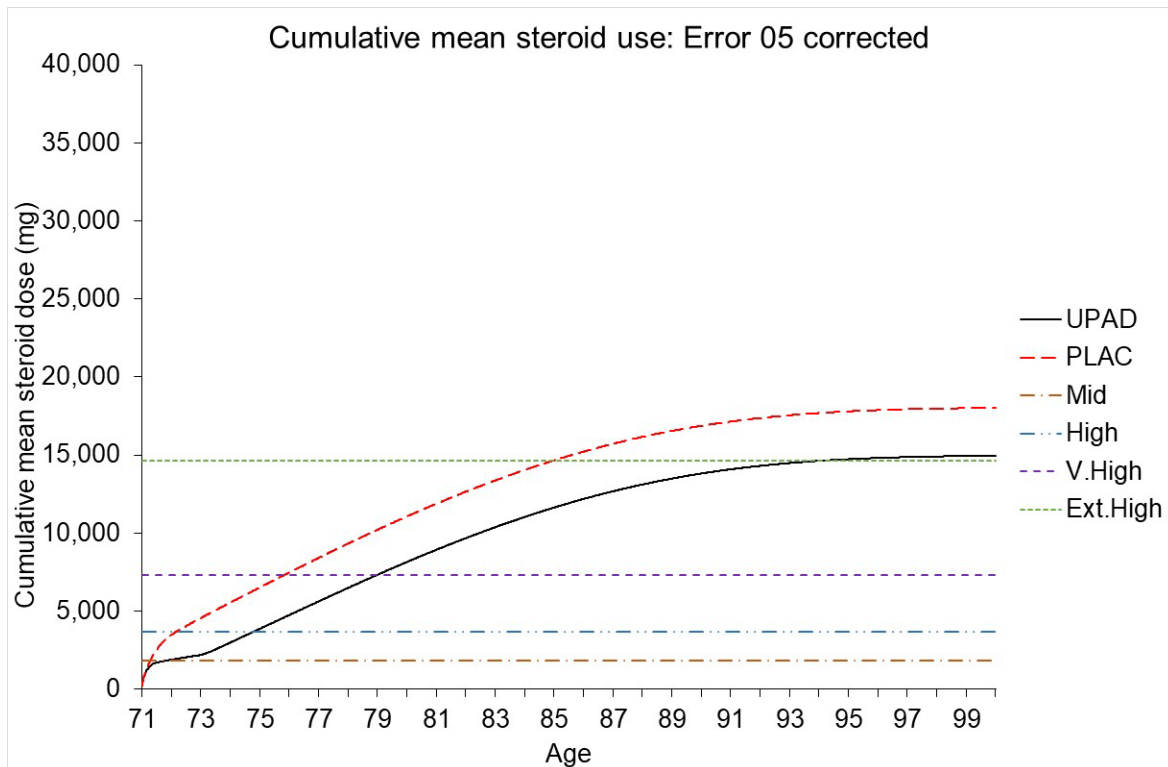


Figure 51: Company ITT base case cumulative steroid dose per surviving patient: Error 05 corrected

Applying the placebo 52 week tapering schedule in the upadacitinib arm from when upadacitinib treatment is stopped results in a smaller reduction in the cumulative steroid dose from upadacitinib with this being roughly maintained over patients' lifetimes rather than continuously increasing as in Figure 60. Patients in the upadacitinib arm are at high risk and very high risk around 3 years later than those in the placebo arm. But the tapering off in the daily steroid dose due to it not being conditioned by the proportion surviving causes patients in the upadacitinib arm to only cross into being at extremely high risk age 94 years, a little under 9 years later than those in the placebo arm.

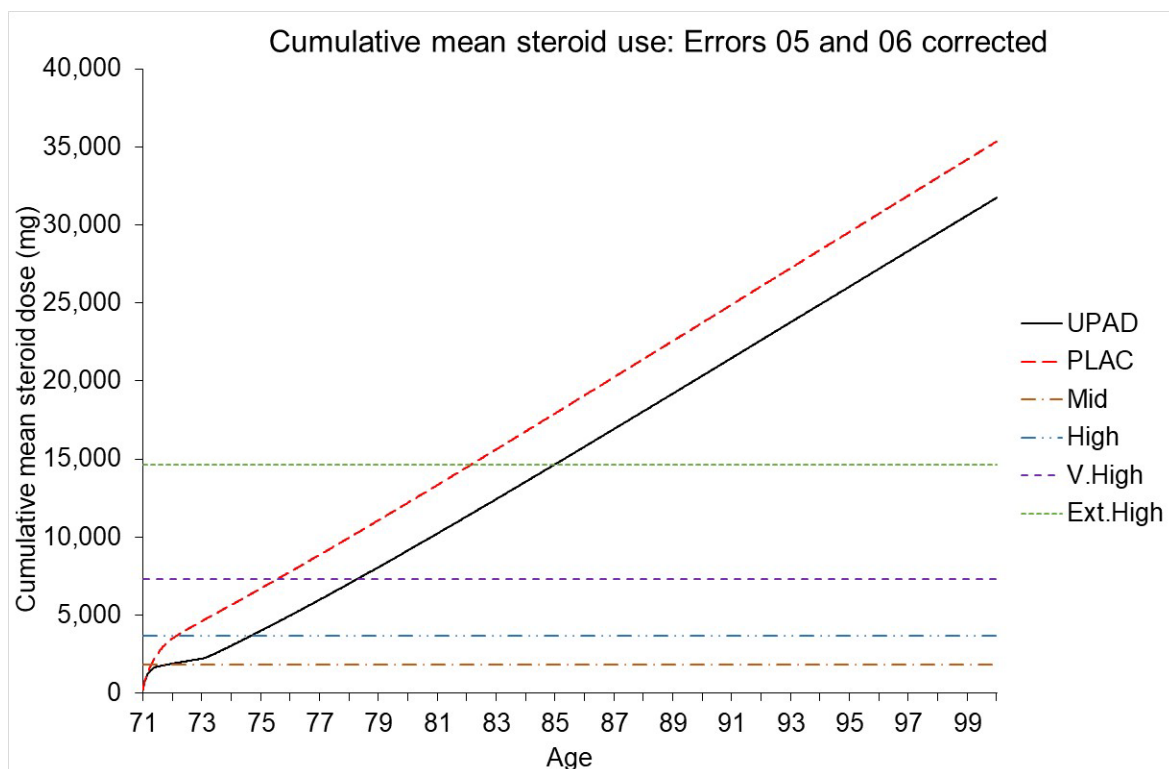
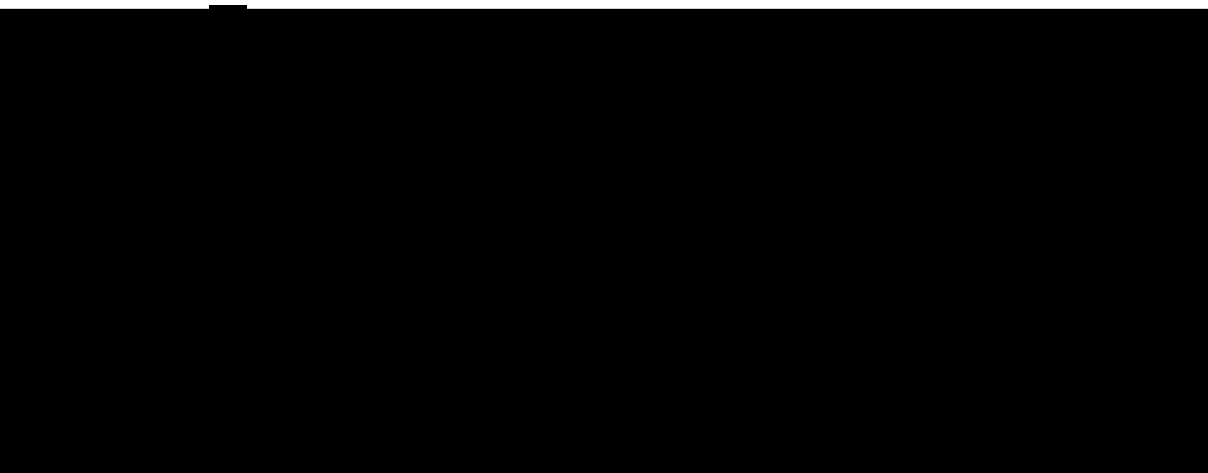


Figure 52: Company ITT base case cumulative steroid dose per surviving patient: Errors 05 and 06 corrected

Figure 61 illustrates the total cumulative steroid dose per surviving patient given the corrections of Errors 05 and 06. The EAG thinks that this is intuitive given an assumption of equal tapering duration and equal probabilities of first and subsequent flares in both arms after cessation of upadacitinib treatment at 2 years. The delays in crossing the high, very high and extremely high risk boundaries are 2.5 years, 2.7 years and 2.8 years respectively.

For the relapsed subgroup the equivalent of [REDACTED] looks much the same, only with the curves shifted up by around 4,500 mg due to their modelled baseline cumulative dose to date.

For the new onset subgroup because the TTFF Gompertz curves results in an indefinite net gain from upadacitinib of [REDACTED] of patients never flaring so not being



3.2.6.10 Adverse events associated with upadacitinib use

While on upadacitinib patients can experience the JAK related adverse events of MACE, major adverse cardiovascular event, and VTE, venous thromboembolism. None were not observed during SELECT-GCA and estimates are taken from a compilation of SELECT studies⁷⁵ yielding an annual probability of 0.6% for both MACE and VTE.

The total cost and QALY loss per event are presented in Table 32 for ease of reference. Costs are taken from Kent et al⁷⁶ for MACE and from an average of NHS reference costs for VTE. QALY estimates for MACE are taken from TA599, sodium zirconium cyclosilicate for treating hyperkalaemia, and for VTA from TA607, rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease.

Both MACE and VTE are assumed to be transient with no long-term effects.

Table 32: Upadacitinib JAK adverse events' probability, cost and QALY

Event	Annual Prob.	Cost	QALY
MACE	0.6%	£5,871	-0.050
VTE	0.6%	£1,739	-0.111

3.2.7 Discontinuations

In the upadacitinib arm patients remain on upadacitinib for 2 years then have it stopped. Thereafter the placebo arm risks of first flares and subsequent flare are applied in the upadacitinib arm.

3.2.8 Health related quality of life

3.2.8.1 Main quality of life values

The quality of life values for the main health states are taken from SELECT-GCA EQ-5D data, pooling data between the arms and using a generalised linear mixed model taking into account repeated measures with baseline EQ-5D as a fixed effect. This results in the quality of life values of Table 33.

Table 33: Quality of Life: No flare and with flare

	ITT	New onset	Relapsed
No flare	0.7685	■	■
With flare	0.7098	■	■
Flare decrement	0.0587	■	■

3.2.8.2 Conditions related to GCA flares quality of life

For ease of presentation and reasons of space the quality of life effects of conditions related to GCA flares are presented alongside their annual probabilities in section 3.2.6.7 above.

3.2.8.3 Conditions related to steroid use quality of life

For ease of presentation and reasons of space the quality of life effects of conditions whose incidence risks are exacerbated by steroid use are presented alongside their annual probabilities in section 3.2.6.8 above.

3.2.9 Resources and costs

3.2.9.1 Direct drug costs

The direct drug costs (Table 34) of upadacitinib are based upon the list price for 28 tablets of £805.56 having a ■ discount applied giving a pack cost of ■. One

pack is sufficient for four weeks hence a per cycle cost of [REDACTED] and an annual cost of [REDACTED]. The model assumes 12 weekly blood tests, liver function tests and lipid panels which add a minor £0.50 to the weekly cost while receiving upadacitinib.

The scope specifies that tocilizumab should be considered. This is available in its original form Roactemra® and the biosimilar Tyenne®.

Table 34: Direct drug costs

	Dosing		Packaging			Annual	
	Dose	Days	mg	Units	Cost	Packs	Cost
Upadacitinib	15 mg	1	15	28	[REDACTED]	13.04	[REDACTED]
Tocilizumab							
Roactemra®	162 mg	7	162	4	£913.12	13.04	£11,911
Tyenne®	162 mg	7	162	4	£821.81	13.04	£10,720

Confidential discounted prices apply to both forms of tocilizumab. The EAG supplies a cPAS appendix that compares annual costs inclusive of discounts.

3.2.9.2 Steroid costs: Error07

Steroids are costed per mg based upon an unweighted average of prednisolone eMIT unit costs (Table 35).

Table 35: Prednisolone costs per mg

	mg	Pack size	Cost	£/mg	Mkt share
..	1	28	£0.29	£0.010	6%
Gastro-resistant	2.5	28	£0.78	£0.011	1%
Gastro-resistant	2.5	30	£0.80	£0.011	0%
..	25	56	£12.78	£0.009	1%
Gastro-resistant	5	28	£0.91	£0.006	1%
Soluble	5	30	£40.70	£0.271	1%
..	5	28	£0.41	£0.003	91%

Simple average		£0.046
Weighted average		£0.006

Error 07: The simple average costing gives undue weight to the soluble formulation which has a unit cost 47 times the weighted average but less than 1% of the market. This results in a cost that is 8 times too large. A weighted average should be applied.

3.2.9.3 Administration and monitoring costs

Rates of resource use are taken from the TA518 company market survey, which is largely undocumented in TA518. For those not in flare this estimated the balance between different types of visit (Table 36).

Table 36: Balance and costs of different types of visit when not in flare

	Balance	Unit cost
Rheumatologist	65%	£181
GP	17%	£49
Geriatrician	10%	£367
Ophthalmologist	5%	£126
Neurologist	2%	£235
Other	1%	£170
Average cost per visit		£176

The survey also provides the average number of visits per month: 1.4 for those in remission and tapering, 0.2 for those in remission who have completed tapering and 0.7 for those post subsequent flare who are tapering. To arrive at an estimate for number of visits for those post flare who have completed tapering the company assumes the same ratio as for those in remission, yielding 0.3 visits. Assuming that the number of visits is equally distributed across the types of visit this resulted in the following resource use (Table 37).

Table 37: Balance and costs of different types of visit when not in flare

	Visits	Cost	
	Monthly	Monthly	Weekly
Remission: tapering	1.39	£245	£56.25
Remission: tapering complete	0.17	£29	£6.72
Post flare: tapering	0.75	£132	£30.27
Post flare: tapering complete	0.32	£57	£13.05

Upadacitinib results in cost savings due to its shorted 26 week tapering schedule.

For those in flare the survey suggests an average of 2.71 visits per flare, the distribution between visits differing for the first visit and the subsequent average 1.71 visits (Table 38).

Table 38: Balance and costs of different types of visit when in flare

	First visit	Subsequent	Unit cost
Rheumatologist	25%	67%	£181
GP	58%	44%	£49
Geriatrician	2%	13%	£367
Ophthalmologist	7%	10%	£126
Neurologist	1%	6%	£235
Other	7%	5%	£170
Average cost per visit	£103.68	£226.11	

The total cost of £103.68 and 1.71 times £226.11 of £490.33 is divided across the assumed 4 week flare duration to give a weekly cost while in flare of £122.58.

3.2.9.4 Conditions related to GCA costs

For ease of presentation the costs of conditions related to GCA flares are presented alongside their annual probabilities in section 3.2.6.7 above.

3.2.9.5 Conditions related to steroid use costs

For ease of presentation the costs of conditions related to steroid use are presented alongside their annual probabilities in section 3.2.6.8 above.

4 COST EFFECTIVENESS RESULTS

4.1 Cost basis

A confidential cPAS appendix that supplies the tocilizumab price discounts and resulting annual costs of treatment has been supplied. Since tocilizumab has not been considered by the company it does not affect any current analyses.

4.2 Company base case cost effectiveness results

For the ITT population the company estimates that upadacitinib saves █████ (Table 39) with a net gain of █████ QALYs (Table 40), so dominates placebo. Probabilistic modelling estimates that upadacitinib has a 100% probability of being cost effective compared to placebo for willingness to pay values between £0 and £100k per QALY.

Table 39: Company base case: Costs

	UPAD	PLAC	Net
Active treatment costs	████	████	████
Steroid costs	████	████	████
Pre-flare remission	████	████	████
Flare	████	████	████
Post-flare remission	████	████	████
GCA complications	████	████	████
GCE complications	████	████	████
JAK complications	████	████	████
Total	████	████	████

Savings in pre-flare remission health state costs are due to the 26-week steroid tapering for upadacitinib compared to the 52-week steroid tapering for placebo, and post steroid health state costs being substantial less than when tapering.

Table 40: Company base case: QALYs

	UPAD	PLAC	Net
Pre-flare remission	████	████	████
Flare	████	████	████
Post-flare remission	████	████	████
Main health states	████	████	████
GCA complications	████	████	████
GCE complications	████	████	████
JAK complications	████	████	████
Total	████	████	████

This results in the cost effectiveness estimates of Table 47.

Table 41: Company base case: Summary

	UPAD	PLAC	Net
Costs	████	████	████
QALYs	████	████	████
ICER			Dominant

At clarification the company presented a revised model which attempts to correct an anomaly, also updating the costs of some conditions. The EAG thinks that addressing the anomaly introduces a further error within the model and so does not apply it within its revised base case. The company model supplied at clarification estimates that upadacitinib results in a █████ QALY gain and saves █████ so is dominant. The EAG does not present the detail of these results due to the model errors summarised in section 4.5.1 below meaning they have little relevance to Committee and decision making. Correcting the model errors worsens the company base case deterministic ICER to £38,359 per QALY. The detailed results of the EAG corrected company base case are presented in section 4.5.1 below.

4.3 Company subgroup analysis

For the new onset subgroup, ■ of SELECT-GCA, the company estimates that upadacitinib saves ■ and results in a net gain of ■ QALYs, so dominates placebo. EAG model corrections revise this to a deterministic ICER of £4,614 per QALY.

For the relapsed subgroup, ■ of SELECT-GCA, the company estimates that upadacitinib saves ■ and results in a new gain of ■ QALYs, so dominates placebo. EAG model corrections revise this to a deterministic ICER of £70,797 per QALY.

4.4 Company sensitivity and scenario analysis

The company presents a range of sensitivity analyses in CS section 3.11.3, page 170, and scenario analyses in CS section 3.11.4, page 172, of its submission. All company sensitivity analyses and scenario analyses estimate that upadacitinib remains dominant. The company has not presented a set of sensitivity and scenario analyses for its lightly corrected model submitted at clarification. Given the model errors identified in section 4.5.1 below the EAG thinks these are no longer relevant.

4.5 Model validation and face validity check

4.5.1 EAG cross check model rebuild

The EAG has fully rebuilt the deterministic company model. This has identified a number of errors. Each error biases the analysis in favour of upadacitinib.

- **Error 01:** Not taking into account baseline cumulative steroid use, which will not be zero due to the proportion of relapsed patients within the ITT population having an average duration of GCA of ■ days.
- **Error 02:** Only those on steroids have a risk of conditions whose incidence can be exacerbated by steroid use, despite these risks being assumed to be a function of the lifetime cumulative steroid use to date.

- **Error 03:** The calculation of the incidences of permanent conditions does not take into account their prevalences.
- **Error 04:** The conversion of annual incidences to weekly incidences is based upon a survivor analysis rather than dividing the annual incidence by 52.³
- **Error 05:** When upadacitinib has been stopped at 2 years the 26-week tapering period is retained rather than switching to the 52-week tapering period.
- **Error 06:** Not conditioning the mean steroid dose for a model cycle by the proportion surviving before adding it to the mean lifetime cumulative dose.
- **Error 07:** Applying a simple average for the cost of prednisolone rather than weighting it by market share.

The EAG corrects for previous steroid use by running the model for the new onset assuming no prior steroid use, and taking the ■■■ day steroid usage estimates and applying these to the relapsed subgroup. The resulting weighted averages provide the baseline values for the ITT population.

The results of correcting these errors are presented in Table 42. Since Error 02 and Error 06 can be viewed as being bound up together their joint effect is also presented.

The EAG corrected company base case ICER is considerably different from the uncorrected ICER so the EAG also presents the effects of disapplying the individual EAG corrections. Some changes, such as Error 01 that applies a mean baseline cumulative steroid dose, appear of minor importance when applied to the uncorrected company base case but are more important when disapplying to the EAG corrected company base case.

Table 42: EAG corrected company base case: Disaggregate cost offsets

	Section	Δ Cost	Δ QALY	ICER
Company base case	4.2	■■■	■■■	Dom
Error 01: Baseline total steroid dose	3.2.3	■■■	■■■	Dom
Error 02: Cohort risks of conditions	3.2.6.8	■■■	■■■	Dom

³ Note that neither method takes into account the proportions of patients dying each cycle.

Error 03: Condition prevalences	3.2.6.8	████	████	Dom
Error 04: Condition incidences	3.2.6.8	████	████	Dom
Error 05: Placebo tapering off Tx	3.2.6.9	████	████	Dom
Error 06: Steroids used cond. by OS	3.2.6.9	████	████	Dom
Errors 02 and 06 together	..	████	████	Dom
Error 07: Prednisolone cost	3.2.9.2	████	████	Dom
EAG corrected company base case	..	████	████	£38,359
Corrected without Error 01	3.2.3	████	████	£29,538
Corrected without Error 02	3.2.6.8	████	████	£4,171
Corrected without Error 03	3.2.6.8	████	████	£7,522
Corrected without Error 04	3.2.6.8	████	████	£35,424
Corrected without Error 05	3.2.6.9	████	████	£13,824
Corrected without Error 06	3.2.6.9	████	████	£36,937
Corrected without Errors 02 and 06	..	████	████	£3,945
Corrected without Error 07	3.2.9.2	████	████	£37,425
Dom = Dominant; i.e. upadacitinib costs less and provides QALY gains				

The health states and complications that contribute at least 3% of the █████ cost offset to the █████ upadacitinib treatment cost are presented in Table 43. Around half the cost offset arises from avoiding flare and post flare remission, the latter being in part determined by the shorter 26-week tapering schedule for upadacitinib.

Table 43: EAG corrected company base case: Disaggregate cost offsets

	UPAD	PLAC	Net	% Offset
Post flare remission	████	████	████	████
Flare	████	████	████	████
Other conditions related to GCA and steroid use				
Glaucoma	████	████	████	████
Type 2 diabetes	████	████	████	████
Dyspnoea	████	████	████	████
Ulcer/GI bleed	████	████	████	████
Major stroke	████	████	████	████

Endocrine adrenal insufficiency	■	■	■	■
Severe infection: hospitalizations	■	■	■	■
Sleep disorders	■	■	■	■
Minor stroke	■	■	■	■
Total	■	■	■	■

The health states and complications that contribute at least 3% of the net QALY gain are presented in Table 44, the totals including all complications. Around a third of the net QALY gain is due to spending more time in remission and less time in flare, with the GCA complications and steroid complications providing the rest. JAK complications from upadacitinib use have minimal impact. All the complications contributing at least 3% of the net gain are steroid related, with the exception of major stroke.

Table 44: EAG corrected company base case: Disaggregate QALYs

	UPAD	PLAC	Net	% Total
Main health states	■	■	■	■
Complication				
Osteoporosis	■	■	■	■
Glaucoma	■	■	■	■
Major stroke	■	■	■	■
Type 2 diabetes	■	■	■	■
Dyspnoea	■	■	■	■
Ulcer/GI bleed	■	■	■	■
Sepsis	■	■	■	■
Hypertension	■	■	■	■
Sleep disorders	■	■	■	■
Severe Infection: hospitalisation	■	■	■	■
Total	■	■	■	■

Costs and QALYs are summarised in Table 45 and Table 46.

Table 45: EAG corrected company base case: Costs

	UPAD	PLAC	Net
Active treatment costs	████	████	████
Steroid costs	████	████	████
Pre-flare remission	████	████	████
Flare	████	████	████
Post-flare remission	████	████	████
GCA complications	████	████	████
GCE complications	████	████	████
JAK complications	████	████	████
Total	████	████	████

Savings in pre-flare remission health state costs are due to the 26-week steroid tapering for upadacitinib compared to the 52-week steroid tapering for placebo, and post steroid health state costs being substantial less than when tapering.

Table 46: EAG corrected company base case: QALYs

	UPAD	PLAC	Net
Pre-flare remission	████	████	████
Flare	████	████	████
Post-flare remission	████	████	████
Main health states	████	████	████
GCA complications	████	████	████
GCE complications	████	████	████
JAK complications	████	████	████
Total	████	████	████

This results in the cost effectiveness estimates of Table 47.

Table 47: EAG corrected company base case: Summary

	UPAD	PLAC	Net
Costs	████	████	████

QALYs			
ICER	-	-	£38,359

The EAG corrected company base case cost effectiveness estimate for the ITT population is £38,359 per QALY. Probabilistic modelling results in a central estimate of £42,863 per QALY and probabilities of upadacitinib being cost effective at willingness to pay values of £20k, £30k, £50k and £100k per QALY of 12%, 28%, 61% and 93% (Figure 63).

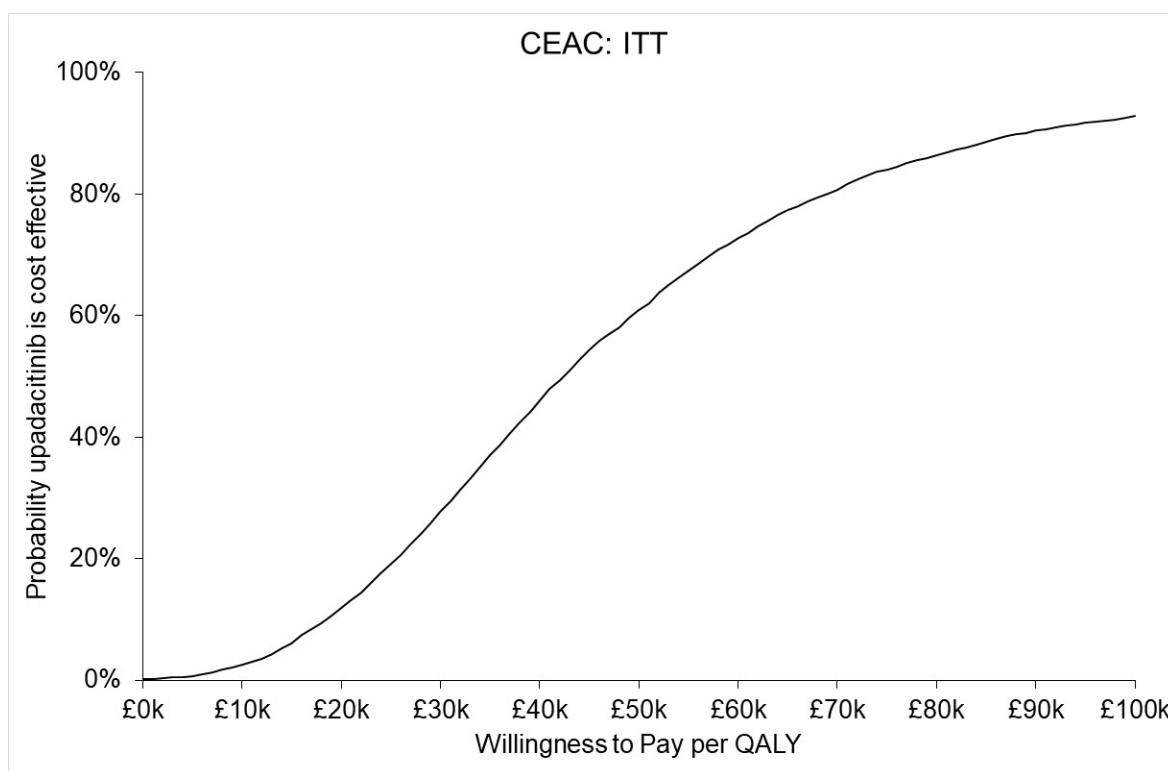


Figure 54: EAG corrected company base case CEAC

In section 5 below unless otherwise stated the effects of EAG model revisions are presented relative to the EAG corrected company base case of £38,359 per QALY.

4.5.2 EAG corrected company base case: Scenario analyses

The EAG presents a subset of the company scenario analyses plus an additional scenario analysis of 1 year treatment duration due to upadacitinib no longer being estimated to dominate for the EAG corrected company base case.

Table 48: Scenarios around EAG corrected company base case

	Δ Costs	Δ QALYs	ICER
EAG corrected company base case	████	████	£38,359
No severe flares	████	████	£24,353
Severe flares restart at 60mg	████	████	£41,162
1 year treatment duration	████	████	£20,650
3 year treatment duration	████	████	£51,623
5 year treatment duration	████	████	£70,669
1 year treatment waning effect	████	████	£33,130
10 year time horizon	████	████	£40,809
20 year time horizon	████	████	£38,065

4.5.3 Model validation

Elements of model validation are presented alongside more general critiques in:

Section 5.2.2: The choice of TTFF curves and modelled proportions flare free for the new onset subgroup.

Section 5.2.7: The SELECT-GCA incidences of conditions the risks of which are exacerbated by steroid use compared to the company market survey that is used for model inputs.

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

5.1 EAG critique of economic modelling compared to position sought

5.1.1 What is the relevance of the company base case economic modelling?

During FAC the company stated that its base case with a stopping rule of 2 years, or treatment duration in the preferred language of the company, was just a scenario analysis much as per the other scenarios around the stopping rule. During FAC the company states that a stopping rule should not be applied.

The longer the treatment duration of upadacitinib the worse its cost effectiveness. The EAG revised base case ICERs for different stopping rules for the ITT modelling are:

1 year £35,371 per QALY

2 years £57,558 per QALY

3 years £74,825 per QALY

5 years £100,612 per QALY

No stopping rule £150,381 per QALY

The company assertion that there should be no stopping rule means that the company base case is largely irrelevant to decision making.

5.1.2 SELECT-GCA Period 2 data

The EAG requested SELECT-GCA Period 2 Kaplan Meier TTFF and TTSF data. The company response was that *"This cohort included patients who received upadacitinib during Period 1 and achieved remission for at least 24 weeks prior to Week 52 (end of Period 1), after which they were re-randomised to either continue upadacitinib or switched to placebo. As such, these patients reflect a pre-selected population with sustained response and are not informative to the economic model"*.

The EAG is surprised that no Period 2 data on TTFF and TTSF has been presented within the submission. It is unusual for longer term trial data to be available but not be presented. During the factual accuracy check (FAC) the company stated that

Period 2 data was not available; the topline data would be available but did not specify when. The company submission states that Period 2 ended March 2025.

The EAG agrees that Period 2 data could be difficult to formally work into the economic model. Yet it might be reasonable or certainly worth exploring, given that the economic model models the proportion who are flare free which at the end of the first year may broadly correspond with the entry criteria to Period 2 of SELECT-GCA.

None of the above implies that Period 2 data is uninformative. For instance, assessing whether there is a greater effect, a similar effect or a lesser effect from upadacitinib compared to placebo among those achieving remission during Period 1 in terms of avoiding flares might help Committee assess the desirability of a 1 year stopping rule compared to a 2-year stopping rule. If there is little effect in Period 2 a 1 year stopping rule could save half the [REDACTED] upadacitinib cost per patient.

The EAG thinks that Period 2 Kaplan Meier TTFF and TTSF data should be presented, as requested under EAG clarification question A15.

5.1.3 Model structure and treatment sequencing

The company model does not consider treatment sequencing, despite separately considering the new onset and the relapsed subgroups and having TTFF and TTSF data specific to these subgroups.

EAG expert opinion suggests that perhaps around 40% of new onset patients will successfully taper their steroids and not flare again. This is in line with the TA518 FAD of 30% to 50% not flaring by 5 years based upon longitudinal data.⁷⁷ The TA518 FAD also noted expert opinion that among those successfully tapering steroids 25% would be flare free at 10 years, though it is unclear if this is specific to new onset patients.

For the new onset subgroup using upadacitinib from GCA diagnosis may not be cost effective compared to using it from second flare in much the same position that tocilizumab was recommended in TA518.

Steroids are much cheaper than upadacitinib. The first two years direct drug costs in the company base case are £203 in the placebo arm and [REDACTED] in the upadacitinib arm, a net cost of [REDACTED]. Using upadacitinib from GCA diagnosis incurs the additional drug cost of [REDACTED] to little or no effect among the 40% or so who would otherwise have successfully tapered their steroids and not flared again. Balanced against this there would be:

- some immediate steroid sparing effect during initial tapering among the 40% or so who successfully taper and do not flare: 1,267mg based upon SELECT-GCA tapering schedules; and,
- some avoidance of or delay in the time to 1st flare post diagnosis among the 60% or so who do flare on or after tapering their steroids.

The EAG notes that the modelling for the new onset subgroup could compare:

- Upadacitinib use from diagnosis⁴
- Upadacitinib use from 1st flare post diagnosis
- Tocilizumab use from 1st flare post diagnosis
- Placebo

During FAC the company stressed that modelling treatment sequencing would depend upon highly uncertain assumptions, though then further noted that the relapsing cohort already captures the post flare experience for patients who progress on steroids alone.

5.2 EAG critique of elements of the company model

5.2.1 Age at baseline

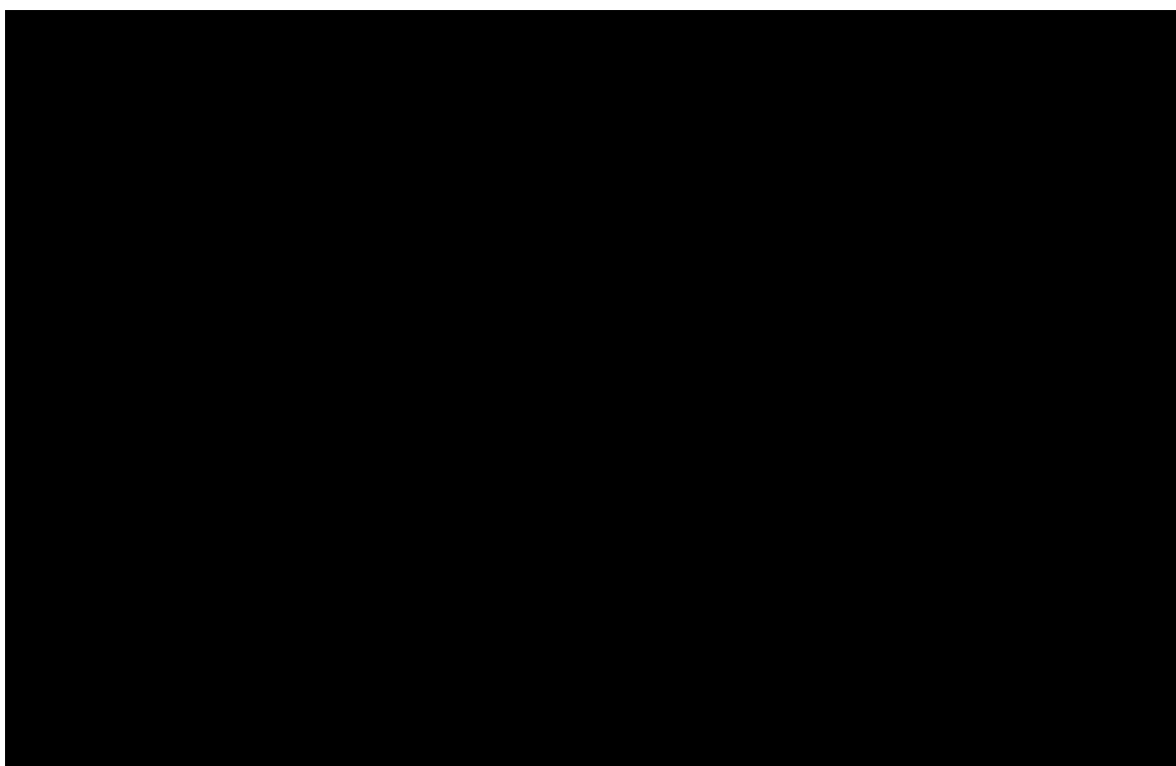
During TA518 age at baseline was an issue. The Committee preferred an estimate of 73 years based upon UK CPRD data. The EAG will apply this in its exploratory base case. The effect is limited, it worsening the EAG corrected company base case from £38,359 to £38,725 per QALY. The effect on the EAG corrected company base case for the new onset subgroup is larger, worsening it from £4,614 to £6,096 per QALY.

⁴ The phrasing of from diagnosis may be a little loose. From start of steroid tapering might be more accurate. But even this may not be quite correct given that patients may be in flare at diagnosis, put onto upadacitinib but steroid tapering not commenced until the flare is under control. That said, the Kaplan Meier data is censored for not being in remission at baseline.

5.2.2 New onset modelling choice of TTFF curves

As outlined in section 3.2.6.3 the company base case for the new onset subgroup applies the Gompertz curves to model the time to first flare. When extrapolated this is radically different from the lognormal curves that the company prefers for its modelling of the ITT and the relapsed subgroup.

The proportions modelled as being flare free for the new onset subgroup and for the relapsed subgroup, the latter retaining log-normal TTFF curves, can be pooled to yield the estimates that are implied for the ITT population. [REDACTED] presents the company base case proportions flare free for its ITT base case, and pooled across its new onset and relapsed base cases.



55

The new onset subgroup is [REDACTED] of the ITT population. As a consequence, the Gompertz curves selected for its base case drive the pooled analysis. Pooling the modelled TTFF curves for the new onset subgroup with those of the relapsed subgroup results in proportions that are very different from the ITT analysis. In terms

of TTFF the pooled subgroup analysis is substantially more favourable to upadacitinib than the ITT analysis.

The company preferred curves for the subgroup modelling result in EAG corrected company base case ICERs of £4,614 per QALY for the new onset and £70,797 per QALY for the relapsed, which when combined result in a pooled estimate of £24,613. This is substantially below the EAG corrected company base case ICER of £38,359 per QALY for the ITT population.

If the lognormal curves are selected for the new onset patients, the pooled analysis curves and the ITT curves for time to first flare coincide. It revised the EAG corrected company base case ICER of £4,614 per QALY for the new onset group to £24,344 per QALY, this in turn yielding a pooled ICER of £38,381 per QALY, which is somewhat more aligned with the ITT estimate.

The FAD of TA518 states *“The clinical experts explained that after 10 years, they would expect around 25% of people who had successfully completed a glucocorticoid taper to not have disease relapse ... Longitudinal cohort data also suggest that at 5 years, 30% to 50% of people having glucocorticoids alone will not have disease relapse”*. The EAG assumes that this applies to the new onset subgroup.

For the new onset subgroup flare free patients as a proportion of the baseline population are presented in Table 49 and Table 50.

Table 49: New onset: Proportion of baseline patients that are flare free: upadacitinib

	Year 1	Year 2	Year 3	Year 5	Year 10
Exponential	████	████	████	████	████
Weibull	████	████	████	████	████
Log-normal	████	████	████	████	████
Log-logistic	████	████	████	████	████
Gompertz	████	████	████	████	████
Gamma	████	████	████	████	████
Generalised gamma	████	████	████	████	████

Table 50: New onset: Proportion of baseline patients that are flare free: placebo

	Year 1	Year 2	Year 3	Year 5	Year 10
Exponential	████	████	████	████	████
Weibull	████	████	████	████	████
Log-normal	████	████	████	████	████
Log-logistic	████	████	████	████	████
Gompertz	████	████	████	████	████
Gamma	████	████	████	████	████
Generalised gamma	████	████	████	████	████

The SELECT-GCA Period 1 provides data to Year 1, at which point all the curves have much the same estimates. They only diverge during extrapolation. Compared to the estimates of the TA518 FAD, Table 50 suggests that that the Gompertz may be a bit too optimistic and the log-normal a bit too pessimistic.

For the new onset subgroup flare free patients as a proportion of those surviving are presented in Table 51 and Table 52. These values may be more relevant to expert opinion if this is considering questions such as “*among those with 10 years since diagnosis of GCA what proportion will not have flared at some point*”.

Table 51: New onset: Proportion of surviving patients that are flare free: upadacitinib

	Year 1	Year 2	Year 3	Year 5	Year 10
Exponential	████	████	████	████	████
Weibull	████	████	████	████	████
Log-normal	████	████	████	████	████
Log-logistic	████	████	████	████	████
Gompertz	████	████	████	████	████
Gamma	████	████	████	████	████
Generalised gamma	████	████	████	████	████

Table 52: New onset: Proportion of surviving patients that are flare free: placebo

	Year 1	Year 2	Year 3	Year 5	Year 10
Exponential	████	████	████	████	████
Weibull	████	████	████	████	████
Log-normal	████	████	████	████	████
Log-logistic	████	████	████	████	████
Gompertz	████	████	████	████	████
Gamma	████	████	████	████	████
Generalised gamma	████	████	████	████	████

This provides little guide as to how to best model upadacitinib, other than to note that the upadacitinib flare free proportion is maintained from year 3 if the Gompertz is applied but shows some convergence towards placebo if the log-normal is applied.

With regards the 25% of those who successfully tapered still being remission free at 10 years the EAG assumes this refers to surviving patients; i.e. if 40% of those alive at year 1 have successfully tapered without flaring and 10% of those alive at year 10 have not flared this would correspond with the 25% figure. Among those surviving to 10 years the proportion who successfully completed taper without flaring at year 1 who remain flare free at year 10 is presented in Table 53.

Table 53: New onset: Proportion successfully tapering who are flare free at 10 years

	EXPO	WEIB	LOGN	LOGL	GOMP	GAMM	GGAM
Upadacitinib	████	████	████	████	████	████	████
Placebo	████	████	████	████	████	████	████
EXPO: exponential, WEIB: Weibull, LOGN: Log-normal, LOGL: Log-logistic, GOMP: Gompertz, GAMM: gamma, GGAM: generalised gamma							

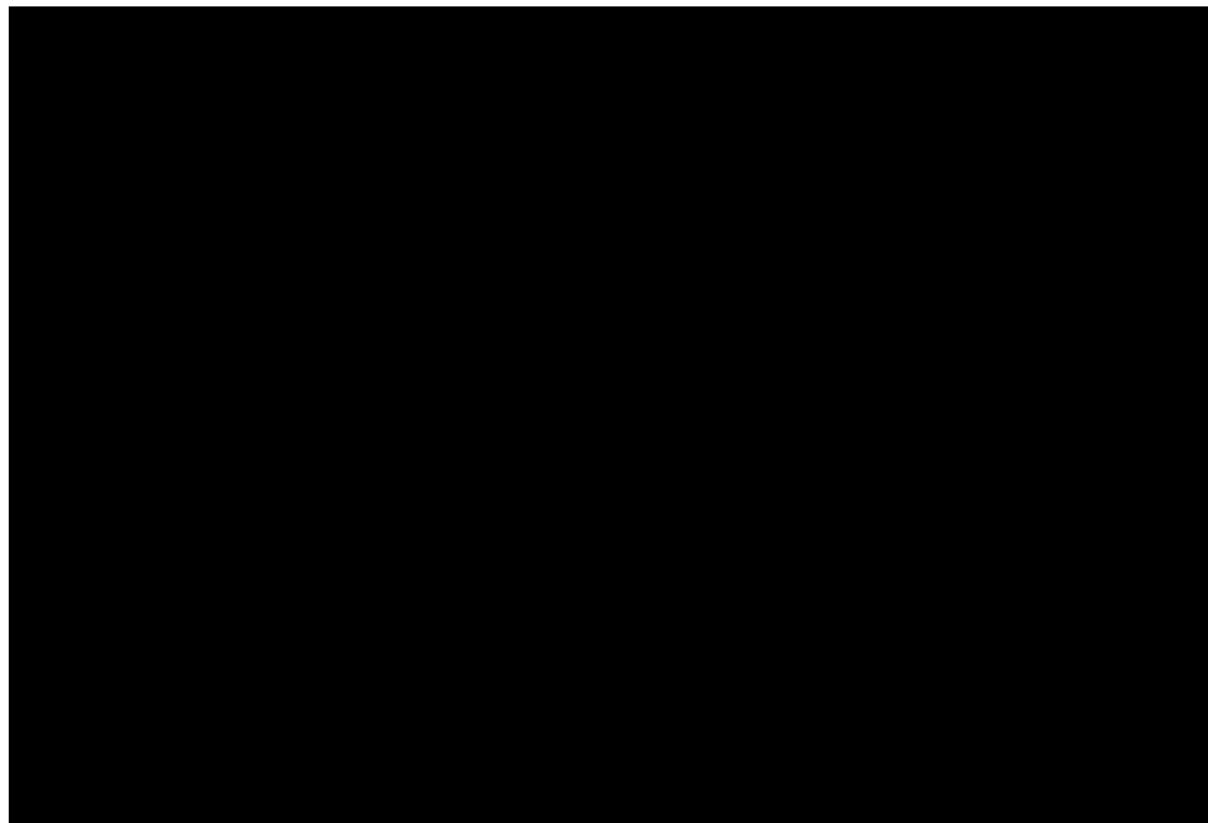
If the EAG interpretation of the TA518 FAD is correct this suggests either the log-normal or the log-logistic curve for modelling the new onset placebo TTFF, though this may again be a little pessimistic. As already noted, if the log-normal TTFF

curves are applied for both the new onset and the relapsed subgroup this results in pooled TTFF curves that are consistent with the ITT log-normal TTFF curves. The clinical review section also notes that the lognormal for the new onset results in proportions that are aligned with the GiACTA trial. Again, this provides no guide as to how best to model upadacitinib.

5.2.3 New onset modelling waning of treatment effect

The company applies the placebo probabilities of flare in the upadacitinib arm from year 2. The company base case for the new onset subgroup applies the Gompertz TTFF curves, but for both upadacitinib and placebo these have little to no probability of flare from year 3. As a consequence, rather than there being a waning of effect the treatment effect is maintained indefinitely.

Waning of effect can be explored by forcing convergence of the TTFF curves over a specified timeframe; e.g. 8 years waning from year 3 as shown in [REDACTED].



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 and the disease path will resume as before. With treatment cessation at 2 years the upadacitinib curve would converge towards the placebo curve over time and may converge completely.

[REDACTED]

Adler et al,⁷⁸ available as an abstract, report results among 30 GCA patients randomized 2:1 to receive tocilizumab or placebo, with tocilizumab being stopped at 52 weeks. The balance between new onset and relapsed is not stated. By week 52 all tocilizumab patients were in sustained complete remission. By week 52 after the last tocilizumab infusion 11 of 20, 55%, patients relapsed with a median time to relapse of 5 months. In the placebo arm 9 out of 10 patients, 90%, either relapsed and/or continued steroid treatment with 1 placebo patient remaining in remission throughout the study. Steroid dosing for major relapse was 1mg/kg, presumably per day, and for minor relapse was 20 to 40 mg per day. The authors conclude that “clinical and serologic remission in response to TCZ for 52 weeks does not result in relapses-free survival after termination of treatment. Although IL-6 blockade using TCZ controls clinical disease, it may not control pathogenesis in all cases”.

Quick et al⁴⁰ invited NHS England rheumatology departments (centres) to participate by submitting anonymised data on all their GCA patients who had completed at least one month of tocilizumab and had at least one follow-up after having stopped tocilizumab. The balance between new onset and relapsed is not stated. Relapse was defined as either documented by the consultant or confirmed by consultant review of medical notes, and as an increase in disease activity sufficient to require a change in treatment plan such as slowing of steroid taper, increase steroid dose or addition of conventional disease-modifying antirheumatic drugs. This permitted inclusion of those not in full remission at cessation of treatment. Median follow-up after treatment cessation was 10 months, but only 8 months among those without a relapse after treatment cessation compared to 15 months for those with a relapse

after treatment cessation. Among the 336 patients they report that around a third had relapsed within one year of cessation of treatment, around a half had relapsed within two years of cessation of treatment and around a third of relapses were major when assessed by the EULAR definition.

The proportion modelled as relapsing after the 2 year stopping rule for upadacitinib when the unwaned Gompertz curve is applied for the new onset and the log-normal for the relapsed appears to be less than the estimates of Alder et al and Quick et al, being approximately 17% and 29% one year and two years after treatment cessation in FIGURE 64. Applying the log-normal curves for both results in a better alignment of approximately 24% and 45%.

The EAG will explore the effects of waning treatment effectiveness as above over admittedly arbitrary periods of 3, 5, 8 and 11 years from year 3.

5.2.4 Incidence of subsequent flares

The incidences of subsequent flares are assumed to be constant. This is despite the probabilities of first flare among the relapsed subgroup declining over time. The duration of data and patient numbers for the collection of subsequent flare data is somewhat less than that for time to first flare and the estimates have quite wide confidence intervals: e.g. for placebo for the new onset subgroup the weekly estimate is [REDACTED]. It can also be noted that the estimates of the incidences of subsequent flares are similar to the initial probabilities of first flare but that the probabilities of first flare decline thereafter.

The EAG will provide scenario analyses that apply the lower and upper confidence bounds of the estimates of the incidences of subsequent flares.

5.2.5 Conditions related to GCA flares

The incidences of aortic aneurism, aortic dissection, myocardial infarction, minor stroke, major stroke or vision loss are assumed to apply only while patients are in flare.

The EAG thinks that some of the cited references yield estimates for GCA patients in general and may not be restricted to those in flare.

For visual loss the estimates of Yates relate to the period 6 months after diagnosis so may be reasonably linked to presentation at diagnosis. They note that 31 of the 33 patients with blindness at six months presented with visual symptoms and only 2 of the 33 developed visual symptoms subsequent to presentation. It is possible that flares subsequent to diagnosis may have a lower probability of visual symptoms or visual loss due to ongoing monitoring and patient awareness of symptoms.

The stroke estimates of Gonzalez-Gay et al relate to newly diagnosed patients and the period between onset of symptoms of GCA and 4 weeks after the beginning of corticosteroid treatment. As a consequence, it seems possible that the four week period assumed when calculating the weekly probability is the minimum that would apply. But the EAG thinks it is probably reasonable to assume that these strokes relate to flare and so attribute them across the 4 week duration of flare.

The above are related to flare at presentation. EAG expert opinion is that the incidences of conditions at presentation are somewhat higher than the incidences of conditions at subsequent flares. This is partly due to patients being investigated and having other conditions diagnosed around the period of GCA diagnosis, but is also due to patients being better educated and receiving much better monitoring and treatment after diagnosis. While 3% having or presenting with stroke on or around diagnosis is reasonable, EAG expert opinion is that the incidence of stroke from subsequent flares will be considerably less. The EAG will present scenario analyses that reduce the incidence of stroke associated with flare to 50% and 25% of the company base case input.

It is assumed that those who are not in flare have no risk of these events. Given the baseline age of 71 years this may not be reasonable.

Amiri et al estimate an incidence rate of 38.1 myocardial infarctions and 26.4 strokes per 1,000 years among patients with GCA, and hazard ratios of 1.77 and 2.21 respectively compared to a matched general population cohort. This suggests incidence rates of roughly 21.5 and 11.9 respectively among the general public, which in turn suggests a net increase in incidence from GCA of 16.6 and 14.5 per 1,000 patient years respectively. The EAG will revise the 38.1 estimate to the net 16.6 per 1,000 patient years. This still appears to relate to GCA patients compared to

the general public, rather than GCA patients in flare compared to GCA patients not in flare.

Akyea et al⁷⁹ analyse UK CPRD data to estimate the incidence of first stroke stratified by age, this ranging from around 500 per 100,000 patient years for those aged 70 to 74 years to around 800 per 100,000 patient years for those aged 85 to 89 years. This is relatively insignificant compared to the 3% incidence among those experiencing flare, but again this is a comparison with the general public.

The difficulty of rates of events at presentation probably being somewhat higher than the rates of events at subsequent flares remains, with no obvious means of addressing it other than arbitrary scenario analyses such as the incidences of major stroke being reduced to 50% and 25% of the company base case input values.

5.2.6 Conditions exacerbated by steroid use and cumulative steroid use

The company cites an as yet unpublished company commissioned paper as the source of its steroid related complications risk estimates. This reports results for steroid mean daily dose classes of less than 7.5mg, 7.5mg to 20mg, 20mg to 40mg and more than 40mg during the year post GCA diagnosis. The company has since reanalysed this data, with the model splitting it by steroid mean daily dose classes of less than 5mg, 5mg to 10mg, 10mg to 20mg, 20mg to 40m and more than 40mg. At clarification the company stated that the reanalysis was due to expert opinion indicating that the original groupings *“did not accurately reflect the way steroid burden is assessed in clinical practice, particularly in the low and medium dose as these ranges were too broad”*. The effects of the reanalysis upon the cost effectiveness estimates is unknown.

For conditions exacerbated by steroid use the company presents the number of new diagnoses of these conditions during the year of diagnosis of GCA stratified by the mean daily steroid dose during the year of diagnosis of GCA. The data for osteoporosis is presented in Table 54 where N is the number of patients, n the number of new diagnoses of osteoporosis in the year of diagnosis of GCA and % the resulting annual incidence.

Table 54: Company incidences of new diagnoses of osteoporosis

Daily dose	N	n	%
Dose $\leq$ 5mg	████	████	████
5mg < dose $\leq$ 10mg	████	████	████
10mg < dose $\leq$ 20mg	████	████	████
20mg < dose $\leq$ 40mg	████	████	████
40mg < dose	████	████	████

The company converts the mean daily steroid doses to cumulative steroid dose cutoffs by multiplying the boundaries by 365.25: 1,826mg, 3,653mg, 7,305mg and 14,610mg.

If the modelled total cumulative steroid dose across the cohort is less than 1,826mg its annual risk of osteoporosis is 6.4%, if between 1,826mg and 3,653mg its annual risk of osteoporosis is 14.5%, etc.. This requires some assumptions:

- The number of new diagnoses in the year of diagnosis of GCA applies to all subsequent years.
- There are no confounding variables.
- While the data relates to one year's steroid use, accumulating a total dose of, say, 2,000mg over one year is assumed to have the same effect upon the risk of events as accumulating a total dose of 1,000mg in year 1 followed by 1,000mg in year 10.
- The effect of steroid use upon the risk of developing a condition is permanent. The risks of developing conditions exacerbated by steroid use for a patient who successfully completes steroid tapering is the same 10 years after having stopped steroid use as on the last day of steroid use.

With regards the first bullet EAG expert opinion is that newly diagnosed GCA patients will have a bone density test and patients with pre-existing osteoporosis will be identified. There will also be routine testing at or around GCA diagnosis for a range of other conditions such as T2DM. Patients will also be encouraged to have a free eye test. The EAG thinks it likely that much of the incidences identified by the

company during the year of GCA diagnosis will be diagnosis of pre-existing conditions rather than new incidence cases caused by steroid use.

EAG expert opinion suggests that the most comorbid are often contraindicated to some treatments and so tend to be those with the highest steroid dose, suggesting that confounding variables may be an issue.

During FAC the company also drew attention to studies which suggested that within six months of stopping steroids the effect of steroids on the incidence some events abated and fell back to the baseline risk. To avoid repetition these papers are summarised in section 5.2.7.

EAG expert opinion also suggests that associating an increased risk with the total cumulative steroid dose since baseline may be reasonable for conditions where the damage is permanent, such as osteoporosis. But it is less reasonable for conditions the risks of developing which abate after steroid use is stopped, EAG expert opinion suggesting the following conditions: electrolyte disorders, palpitations, GI perforation, ulcer/GI bleeds, gastritis, infections, sepsis, sleep disorders, dyspnoea, acne, hirsutism, endocrine adrenal insufficiency, Cushing's syndrome, myopathy, heart failure, hyperlipidaemia, aseptic necrosis of the bone, raised IOP and glaucoma. The EAG explores revising the risks of these to be dependent upon the total steroid dose of the previous year rather than the total steroid dose since diagnosis.

5.2.7 Conditions exacerbated by steroid use: SELECT-GCA placebo arm compared to company market survey

At clarification (B4), the company provided data on the SELECT-GCA end of Period 1 placebo arm proportions of patients with the modelled conditions. The company was asked that baseline prevalences and new diagnoses during Period 1 be presented separately, and separately by arm. Only one set of SELECT-GCA data was presented, that for the placebo arm. These are new diagnoses during Period 1 and exclude conditions prevalent at baseline.

Due to the average total steroid use in the placebo arm being 2,882 mg during Period 1 the company compares this data with the risk category of its market survey data related to a cumulative dose of 1,826 mg to 3,653 mg.

Note that the 2,882 mg cumulative steroid dose does not take into account prior steroid use among the relapsed. Given the average duration of GCA of █ days among the relapsed the model suggest an additional 4,352 mg steroid use among the relapsed which would add 1,322 mg to the ITT mean cumulative dose taking it to 4,204 mg and into the next higher risk category of 3,653 mg to 7,305 mg. This would further increase the ratios reported in Table 55.

A subset of the more important conditions exacerbated by steroid use as identified in or related to those of Table 43 and Table 44 is presented in Table 55, with the full set of conditions presented in Table 71 in Appendix 3.

Table 55: Subset of conditions exacerbated by steroid use: SELECT-GCA vs company market survey

SELECT-GCA placebo arm		Company market survey		Ratio
Sleep disorders	█	Sleep disorders**	█	█
Type 2 diabetes	█	Type 2 diabetes*	█	█
Hypertension	█	Hypertension**	█	█
GI perforation	█	GI perforation*	█	█
Ulcers	█	Ulcer/GI bleed*	█	█
Gastritis	█	Gastritis*	█	█
Sepsis	█	Sepsis*	█	█
Dyspnoea	█	Dyspnoea*	█	█
Adrenal suppression	█	Endoc. adrenal insuff.*	█	█
Serious infections	█	Infection Hosp:	█	█
Osteoporosis	█	Osteoporosis**	█	█
IOP increased	█	Increased IOP*	█	█
Glaucoma	█	Glaucoma**	█	█
* Newly diagnosed, ** Newly diagnosed and treated ⁵				
Infection Hosp: Infection requiring hospitalisation				

The company notes that a true mapping between events was not possible due to SELECT-GCA using the MedDRA 26.1 classification system the while the market

⁵ Within the clarification response it is unclear whether “newly diagnosed or treated” means “treated and/or newly diagnosed” or “newly treated and/or newly diagnosed”. The EAG reading of the market survey report is that it is “newly treated and/or newly diagnosed”.

survey uses the ICD10, stating that *“Due to the differences in structure, purpose and granularity, and the requirement of a clinician with in-depth knowledge, AbbVie is unable to map the adverse events observed in SELECT-GCA to ICD10 codes”*.

In general, the company market survey estimates rates that are multiples of those observed in the SELECT-GCA placebo arm. There are exceptions, most notably serious infections, but some of the discrepancies may be due to differing definitions: e.g. SELECT-GCA reporting serious infections but the market survey reporting severe infections resulting in hospitalisation.

When presenting the data of Table 55 company clarification response states that *“the overall adverse event rates and corticosteroid-related adverse events in SELECT-GCA, along with those from other randomised controlled trials, do not fully capture the long-term risks associated with corticosteroid exposure. This limitation is due to the controlled trial environment, the relatively short follow-up period of 52 weeks, and the chronic nature of many corticosteroid-related adverse events”*. The EAG disagrees with much of this in relation to Table 55 because:

- None of the data of Table 55 relates to the long term risks of steroid use. The market survey data is of 1 year’s duration from diagnosis of GCA and the SELECT-GCA data is of 1 year’s duration so the two are quite well aligned. It can be noted that the market survey data is specific to the newly diagnosed so it would have been more appropriate for the company to present SELECT-GCA data for the new onset subgroup⁶. But given the ratios and that the new onset subgroup was ■ of the ITT population this seems unlikely to change the overall picture.
- The controlled nature of clinical trials and frequency of patient follow-up might be expected to identify more rather than fewer incidences of conditions exacerbated by steroid use. While it should be borne in mind that the market survey data is based upon US data, this does not directly relate to the point in question of trial data versus real world data.

The EAG agrees with the company that longer term data on the incidences of conditions exacerbated by steroid use among GCA patients would be useful. The

⁶ The EAG requested this at clarification

company market survey “*identified patient newly diagnosed with GCA and assessed GC use, 33 GRAE events, healthcare resource utilization (HCRU) and costs for ≥12 months up to 60 months post-GC initiation*”. The EAG asked the company to supply the incidence of conditions data separately for each of the five years since diagnosis stratified by (a) the cumulative steroid dose that year, and (b) the cumulative steroid dose since diagnosis. This could help address the issues identified in section 5.2.6 above: whether the incidences of the conditions during the year of diagnosis of GCA are related more to the diagnosis of GCA and associated investigations than to the steroid use to date, and whether some conditions are better modelled as a function of the previous year’s steroid use rather than the total cumulative steroid use since diagnosis. The company supplied some the data, but not all in the requested format. Data for months 36 to 60 was apparently not available separately by year. It also did not supply the data relating to the control groups. Consequently, the EAG has not been able to incorporate this data.

During FAC the company noted that the difference between the SELECT-GCA data and the company market survey may be due to patients in the real world following a less rigorously defined steroid tapering schedule and not being subject to stringent trial inclusion and exclusion criteria. The EAG notes that this may beg more questions than it answers, particularly about the relevance of SELECT-GCA time to first flare data around which all the modelling revolves.

During FAC the company drew attention to estimates it supplied during clarification of annual risks from papers in the literature for those with a cumulative steroid dose of 2.6 mg to 8.4 mg daily, this being the closest to the 5.0 mg to 10.0 mg classification within the model.

An annual rate of 3.2% for T2DM from Wu et al²⁸ compared to the model input of ■■■. Wu et al analysed UK CPRD data on 100,722 adult patients without diabetes in six immune mediated inflammatory diseases: irritable bowel disease, GCA, polymyalgia rheumatica, rheumatoid arthritis, systemic lupus erythematosus and vasculitis. They note that for daily doses of less than 15 mg adjusted hazard ratios were higher within the year of diagnosis, but that this reversed at higher steroid doses. The cumulative risk of diabetes at 1 year increased from 0.9% for those without corticosteroid use to 2.1% for a daily dose of less than 5 mg, to 5.0% for a daily dose of more than 25mg. Wu et al also report hazard ratios for cumulative

doses, but the EAG is currently unclear whether these relate to the total cumulative doses or to annual cumulative doses. The findings of Wu et al are mirrored by those of Movahedi et al⁸⁰ who estimated a hazard ratio of 1.48 for a 5 mg dose over six months, Movahedi et al also reporting that the hazard ratio returns to 1.00 three months after stopping steroid use, concluding that “doses taken >6 months previously did not influence current risk”. The EAG thinks this suggests that rates of T2DM for those not receiving steroid are not zero, that the modelled increase in T2DM rates is too large and that it is reasonable to assume that the effects of steroid use on the risks of developing T2DM abates after cessation of steroids.

An annual rate of 42.9% for any infection event from Wu et al³² compared to the model input of [REDACTED]. Wu et al analysed UK CRPD data in a similar manner to their T2DM paper, estimating the incidence of infections among 39,938 patients with either polymyalgia rheumatica or GCA. The proportion that was new onset is not stated. Median follow-up was 4.8 years (IQR 2.2-8.5) during which 55.7% of patients had an infection, mostly lower respiratory tract, 27.3%, conjunctivitis, 8.6%, and herpes zoster, 7.4%. For these three types of infection the company did not provide data for lower respiratory tract infections or for conjunctivitis, but only for herpes zoster which may suggest that not all infections included within Wu et al are included within the [REDACTED] model input. The EAG has not been able to find the 42.9% rate of the company but notes that 55.7% over the media 4.8 years suggests an annual rate of 11.6%. Wu et al note that at one year the probabilities of any infection were 12.9%, 18.0%, 21.1%, 30.4% and 35.8% for no steroid use, less than 5 mg, 5 mg to 15 mg, 15 mg to 25 mg and more than 25 mg respectively. Wu et al also provide figures for five years, but these are more difficult to interpret due to the greater possibility of repeat infections. This also needs to be read in conjunction with Dixon et al⁸¹ who estimated a 1.46 odds ratio for the risk of serious infection for a 5 mg dose over six months, and this falling back to 1.06 six months after stopping steroid use, though this latter had a confidence interval of 0.98 to 1.27. Dixon et al also note that the risk of 3 years of 5 mg dosing, or a cumulative dose of 5,475 mg, was similar in effect to that of taking 30 mg for the last month, a cumulative dose during the month of around 910 mg. The EAG thinks this suggests that infection rates for those not receiving steroids are not zero, that the modelled increase in infection rates is too large and that it is reasonable to assume that the effects of steroid use on the risks

of infection abates after cessation of steroids. Additional information on the types of infection included in the company analysis of US insurance data could help align the estimates with those of Wu et al.

An annual rate of 6.2% for cardiovascular events from Pujades-Rodriguez et al²⁹ compared to the model input of [REDACTED]. Within this, rates for MI, non-fatal stroke and heart failure appear similar but it is unclear whether event definitions are completely aligned. Pujades-Rodriguez et al also analysed the UK CPRD database and the same six inflammatory conditions as Wu et al²⁸. The EAG has not been able to source the 6.2% estimate. Pujades-Rodriguez et al report 1 year cumulative incidences of 1.4%, 3.8%, 4.8%, 7.2% and 8.9% for daily doses of none-use, less than 5 mg, 5 mg to 15 mg, 15 mg to 25 mg and more than 25 mg respectively. These are all somewhat less than the model input.

For all the studies briefly summarised above the proportion of patients who were new onset is not stated and the effect of this upon results is not known.

The EAG thinks that the data of Table 55, and of the full set of Table 71, for the upadacitinib arm could provide Committee with estimates of how much the steroid sparing effects of upadacitinib translate into actual patient benefits at 1 year. The equivalent data for Period 2, split by randomisation strata, could also help inform this to the 2 year point, after which it is assumed that upadacitinib use will cease.

Given the major discrepancies of Table 55 the EAG questions whether much if any weight can be placed upon the company modelling of conditions the risks of which are exacerbated by steroid use. This is not to say that steroid use does not have long term consequences, or that there is no benefit from the steroid sparing effect of upadacitinib.

The EAG revised base case will present a scenario analyses which excludes this aspect of the modelling.

5.2.8 Adverse events associated with upadacitinib use

JAK related adverse events are MACE, major adverse cardiovascular event, and VTE, venous thromboembolism were not observed during SELECT-GCA and estimates are taken from a compilation of SELECT studies.⁷⁵ Their impact is assumed to last only one year. This seems surprising given both their potential severity and that the company modelling of myocardial infarction and stroke assumes lifelong effects. Time constraints mean that the EAG has not been able to review these. The EAG exploratory base case assumes that the quality of life effects of MACE are permanent.

5.3 EAG critique of the handling of quality of life within the model

5.3.1 Main quality of life values

The company supplied the raw post baseline SELECT-GCA EQ-5D quality of life values for being in flare and not being in flare at clarification. A simple comparison of the pooled mean values yields a value of [REDACTED] when not in flare which is similar to the company base case GEE estimate of 0.7685. The number of patients supplying quality of life values for being in flare were only [REDACTED] at weeks 8, 24 and 52 respectively. These provide a simple average of [REDACTED] which is above the company base case GEE estimate of 0.7098.

TA518, also using EQ-5D trial data, supplied estimates of 0.7713 for flare free and 0.6420 for being in flare, there being additional values for the new onset and the relapsed.

CS Section 3.4.1, page 137 provides the results of a systematic review of quality of life values, other estimates being within the ranges outlined above.

The EAG will supply scenario analyses that apply the simple SELECT-GCA averages and the TA518 values.

5.3.2 Duration of transient conditions

The quality of life decrements for transient conditions related to GCA flares and transient conditions exacerbated by steroid use are treated as QALY decrements. This implicitly assumes that the durations of these conditions' quality of life effects is one year. This seems unreasonable, particularly since upon diagnoses the conditions will be treated.

EAG expert opinion suggests estimate of around:

- 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.

5.4 EAG critique of the handling of costs within the model

5.4.1 Monitoring costs

The company relies upon the minimally documented TA518 market survey. This suggests that during steroid tapering after remission patients will visit a rheumatologist on average around 0.90 times per month, or approximately once a month.

EAG expert opinion suggests that provided they do not flare the majority of patients, around 75%, will manage with an initial visit and additional visits at 6, 18 and 42 weeks. The remainder will be roughly equally split between those seen initially and at 6, 18, 30 and 42 weeks with an additional wrap up visit, and those being seen monthly. This suggests an average of 0.45 times per month, or approximately every other month. Other EAG expert opinion suggests visits on average only every three

to four months, and also raises the possibility of biologics requiring a couple of visits for nurse training in their use.

The EAG will provide a scenario analysis that halves the monitoring costs.

5.4.2 Costs of conditions related to GCA flare, to steroid use and to upadacitinib use

Given the range of conditions modelled by the company the EAG cannot undertake a full review of each of these. It provides some commentary on the more important unit costs within the EAG corrected company base case.

At clarification (B13) the EAG asked the company to provide a full account of the calculations underlying these costs, including “*the currency codes, speciality, type of patient engagement, e.g. consultant face to face followup, setting, e.g. day patient and OP included, etc*” but this was not provided. As a consequence, there is some EAG conjecture in what follows. The EAG has also been forced to use 2022-23 NHS reference costs due to 2023-24 NHS reference costs being offline at the time of writing.

Major stroke: The company estimates an annual cost of £5,064 based upon NHS reference costs for admission for stroke with a complications and comorbidity score of at least 10. This is multiplied by five to give a five-year cost of major stroke of £25,319; i.e. it is assumed that after being admitted for stroke these patients are admitted an additional four times at the same cost each time. This seems unreasonable but a major stroke is likely to require large rehabilitation costs. Costs within the literature vary. Luqmani et al⁶⁷ report a NICE five-year costing of £29,400 which is somewhat less than Patel et al⁸² who modelled £15,557 first year cost and £5,761 subsequent annual rehabilitation costs yielding a total five year cost of £38,601. Uprating these for inflation suggests a five year cost of between £36,274 and £47,625. The EAG will apply the former for its base case and the latter in a scenario analysis.

Minor stroke: The company estimates an annual cost of £2,170 based upon NHS reference costs for admission for stroke with a complications and comorbidity score of up to 10. As for major stroke, this is multiplied by five to give a five-year cost of minor stroke of £10,848; i.e. it is assumed that after being admitted for stroke these

patients are admitted an additional four times. This seems unreasonable for minor stroke so the EAG only applies the first-year cost of £2,170, though the EAG recognises there will be additional primary care follow up and medication.

Glaucoma: The company estimates a unit cost based upon an average of NHS reference costs £845. Fu et al⁸³ in an analysis of 5 NHS hospital glaucoma clinics and 21,719 patients estimate an average annual cost of £405, though this does not include any primary care costs. The EAG will apply an annual glaucoma cost of £405.

Hypertension: The company estimates a unit cost of £759 based upon an average of NHS reference costs for code EB04Z – Hypertension. This appears to be restricted to the 50,866 patients admitted to hospital for treatment of their hypertension. The annual number of patients treated for hypertension is well in excess of 50,866 with most not being admitted to hospital. The ACE inhibitor captopril has an EMIT cost of £0.85 for a 56 pack of 25mg. Assuming 25mg twice daily yields a drug cost of £11.09. Given the ongoing routine resource use some of this may be prescribed at a routine follow-up or GP appointment, but the cost of a £45 GP appointment might be added to this. £56 is perhaps the lowest reasonable marginal cost that might be applied for hypertension. The EAG views the company £759 as unreasonable so will apply a marginal cost of £56.

T2DM: While T2DM can lead to very high costs this is usually some time after diagnosis. Since these are new diagnoses among a relatively old patient group with an average life expectancy at baseline of around 10 years these higher costs may not be reached by many if any patients. Many patients may have occasional outpatient appointments and be treated with relatively cheap oral anti-diabetic drugs. That said the company average one off cost of £1,680 for “transient” T2DM may not be unreasonable in the light of it being in reality a permanent condition.

Ulcer/GI bleed: The company estimates a unit cost of £1,907 based upon an average of NHS reference costs FD03A to FD03H for treatment of gastrointestinal bleeds. This appears to be based upon 90,627 admitted to hospital for treatment of their gastrointestinal bleed. This ignores the treatment of ulcers which is likely to be less costly. Some of these patients will be referred for gastroscopy at a cost of perhaps £654-£754 based upon admitted patient case FE21Z and FE22Z. Ulcer

treatment may also include gastro-resistant omeprazole at an EMIT cost of £0.33 for a 28 pack of 20mg which if once daily results in an annual cost of £4.30.

The EAG has no information on the balance between GI bleeds and ulcers. The EAG arbitrarily assumes 10% are GI bleeds requiring hospital admittance, partly in light of GI perforations being modelled separately at a cost of £6,195. The remaining 90% are ulcers all requiring a GP appointment and treatment with omeprazole. Further assuming 25% of ulcers require two gastroscopies and one additional GP appointment results in an average cost of £585.

Adrenal insufficiency: The company derives an estimate of £1,922 in 2013 prices from Chauhan et al,⁸⁴ an industry sponsored study of UK patients available only in abstract. 30% of the cost is related to productivity losses which the EAG excludes.

Severe infection: Hospitalized: The company estimates a cost of £4,263 based upon averaging a range of NHS reference costs for non-elective inpatient long stay that include infections in their descriptors. 2022-23 reference costs provide a similar cost for non-elective inpatient long stay of £4,062 but the EAG can see no reason to exclude the non-elective inpatient short stay data which reduces the mean cost to £2,150. As a consequence, the EAG applies an adjustment factor of $2,150/4,062 = 53\%$.

Dyspnoea: The company estimates a cost of £1,667 based upon averaging hospital admission costs for sleep disorders affecting breathing with and without interventions, DZ18D to DZ18G, across a total of only 5,800 admissions. The EAG assumes that many of the usual causes of shortness of breath such as lung cancer do not apply. This makes it difficult to speculate quite what the cost of dyspnoea should be, but it is questionable whether all or indeed many patients would incur the company anticipated resource use. 2022-23 NHS reference costs suggest an average cost per visit to a pulmonary rehabilitation service, WF01A to WF01D, of £93. Assuming one GP appointment and four visits to pulmonary rehabilitation yields a cost of £417.

Sleep disorders: The company estimates a cost of £970 based upon averaging the NHS costs of admissions for sleep disorders, codes AA43A and AA43B which had a total number of admissions during 2023/24 of 2,357. Again, it seems likely that rather more people present with and are treated for sleep disorders than the 2,357 who

were admitted for this under codes AA43A and AA43B. For want of a better estimate the EAG applies its £417 estimate for dyspnoea though this may still be too high.

MACE: Upadacitinib use is associated with a risk of Major Adverse Cardiovascular Events. This is costed at £5,871 based upon updating a 2010 £4,400 cost for MACE within a paper estimating the cost effectiveness of interventions for NSTEMI patients. The £4,400 estimate is based upon Scottish Cardiac Revascularisation Register data on angiograms, PCIs and CABGs combined with NHS reference costs. The authors note that this data is limited in several respects, but few details are provided. Time constraints mean that the EAG does not know whether this costing is representative, but it appears to relate to the immediate costs of NSTEMI treatment. Some or most MACE may involve long term costs, as with stroke. The EAG will provide a scenario analysis that applies the cost of major stroke to MACE events.

5.5 Minor issues

5.5.1 Minor Issue: Baseline steroid distributions

The company base case assumes different baseline steroid distributions between the arms. Pooling data across the SELECT-GCA arms and applying the same baseline distribution in both arms slightly improves the EAG corrected company base case ICER from £38,359 to £38,104 per QALY.

Combining this with subgroup specific baseline distributions worsens the EAG corrected company base case for the newly onset subgroup from £4,614 to £5,854 per QALY. It improves the EAG corrected company base case for the relapsed subgroup from £70,797 to £65,596 per QALY.

5.5.2 Minor issue: Bilateral visual loss costs

The company calculates a unit cost of bilateral visual loss of £66,366 based upon costs in the first year and subsequent year of £6,280 and £6,049, coupled with the mean life expectancy in the upadacitinib arm of 10.9 years. This is correct at baseline but does not take into account decreasing life expectancy thereafter. Applying the costs at the time which they occur reduces the EAG corrected company

base case net savings from avoiding bilateral visual loss from £46 to £44 which has negligible effect upon the ICER.

5.5.3 Permanence of minor stroke

The company assumes that the quality of life effect of minor stroke is permanent. This may not be reasonable. Assuming a 1 year duration of effect worsens the EAG corrected company base case from £38,359 to £39,357 per QALY.

The EAG exploratory base case assumes a 1 year quality of life effect from minor stroke.

company base case this worsens the ICER from £38,359 to £39,357 per QALY.

5.6 Exploratory and sensitivity analyses undertaken by the EAG

5.6.1 EAG model revisions

The EAG makes the following changes to the company base case.

- EAG01: Correcting the model errors identified in section 4.5.1
- EAG02: A baseline age of 73 years
- EAG03: Log-normal time to first flare among the new onset subgroup
- EAG04: Revising the duration of the quality of life effect of some of the transient events to be less than one year
- EAG05: Applying EAG estimates of the costs of some events
- EAG06: Minor issues, this also 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.

Table 56: EAG changes: pairwise cost effectiveness estimates vs placebo

	Section	ITT	New onset	Relapsed
Company Base Case	4.2	Dom	Dom	Dom

EAG01: Model corrections	4.5.1	£38,359	£4,614	£70,797
EAG02: Baseline age 73 years	5.2.1	£38,725	£6,096	£69,414
EAG03: Log-normal time to first flare	5.2.2	..	£23,344	..
EAG04: Transient QoL durations	5.3.2	£46,147	£5,415	£86,560
EAG05: Event costs	5.4.2	£44,129	£8,138	£78,787
EAG06: Minor issues	5.5	£41,206	£6,192	£70,576
EAG base case: EAG01-EAG06	..	£57,558	£42,918	£98,754
Dom: Upadacitinib dominates placebo				

5.6.1.1 EAG exploratory base case: ITT population

The main drivers of the estimated cost offsets are presented in Table 57.

Table 57: EAG base case: Disaggregate cost offsets: ITT

	UPAD	PLAC	Net	% Offset
Post flare remission	████	████	████	████
Flare	████	████	████	████
Other conditions related to GCA and steroid use				
Type 2 diabetes	████	████	████	████
Major stroke	████	████	████	████
Glaucoma	████	████	████	████
Pre-flare remission	████	████	████	████
Sepsis	████	████	████	████
Palpitations	████	████	████	████
Endocrine adrenal insufficiency	████	████	████	████
Opportunistic infections	████	████	████	████
Severe infection: hospitalizations	████	████	████	████
Total	████	████	████	████

The health states and complications that contribute at least 2% of the net QALY gain are presented in Table 58.

Table 58: EAG base case: Disaggregate QALYs: ITT population

	UPAD	PLAC	Net	% Total
Main health states	████	████	████	████
Complication				
Osteoporosis	████	████	████	████
Glaucoma	████	████	████	████
Major stroke	████	████	████	████
Type 2 diabetes	████	████	████	████
Dyspnea	████	████	████	████
Pre-diabetes	████	████	████	████
Vision loss - unilateral	████	████	████	████
Ulcer/GI bleed	████	████	████	████
Hypertension	████	████	████	████
Myopathy	████	████	████	████
Sleep disorders	████	████	████	████
Total	████	████	████	████

Costs and QALYs are summarised in Table 59 and Table 60.

Table 59: EAG base case: Costs: ITT population

	UPAD	PLAC	Net
Active treatment costs	████	████	████
Steroid costs	████	████	████
Pre-flare remission	████	████	████
Flare	████	████	████
Post-flare remission	████	████	████
GCA complications	████	████	████
GCE complications	████	████	████
JAK complications	████	████	████
Total	████	████	████

Table 60: EAG base case: QALYs: ITT population

	UPAD	PLAC	Net
Pre-flare remission	████	████	████
Flare	████	████	████
Post-flare remission	████	████	████
Main health states	████	████	████
GCA complications	████	████	████
GCE complications	████	████	████
JAK complications	████	████	████
Total	████	████	████

This results in the cost effectiveness estimates of Table 61.

Table 61: EAG base case: Summary: ITT population

	UPAD	PLAC	Net
Costs	████	████	████
QALYs	████	████	████
ICER			£57,558

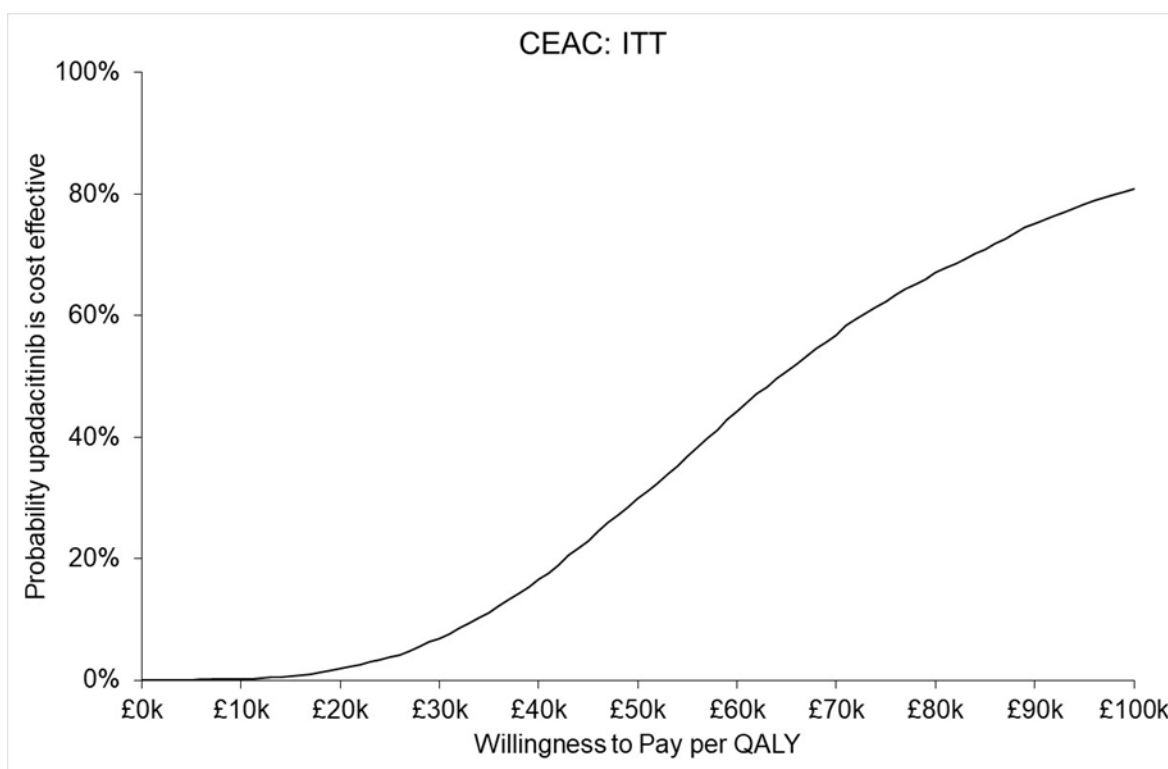


Figure 57: EAG base case: CEAC: ITT population

Probabilistic modelling results in a central estimate of £64,876 per QALY, and probabilities of being cost effective at willingness to pay values of £20,000, £30,000, £50,000 and £100,000 per QALY of 2%, 7%, 30% and 81% respectively (Figure 66).

5.6.1.2 EAG exploratory base case: new onset subgroup

Costs and QALYs are summarised in Table 62 and Table 63.

Table 62: EAG base case: Costs: new onset subgroup

	UPAD	PLAC	Net
Active treatment costs	████	████	████
Steroid costs	████	████	████
Pre-flare remission	████	████	████
Flare	████	████	████
Post-flare remission	████	████	████
GCA complications	████	████	████

GCE complications	■	■	■
JAK complications	■	■	■
Total	■	■	■

Table 63: EAG base case: QALYs: new onset subgroup

	UPAD	PLAC	Net
Pre-flare remission	■	■	■
Flare	■	■	■
Post-flare remission	■	■	■
Main health states	■	■	■
GCA complications	■	■	■
GCE complications	■	■	■
JAK complications	■	■	■
Total	■	■	■

This results in the cost effectiveness estimates of Table 64.

Table 64: EAG base case: Summary: new onset subgroup

	UPAD	PLAC	Net
Costs	■	■	■
QALYs	■	■	■
ICER			£42,918

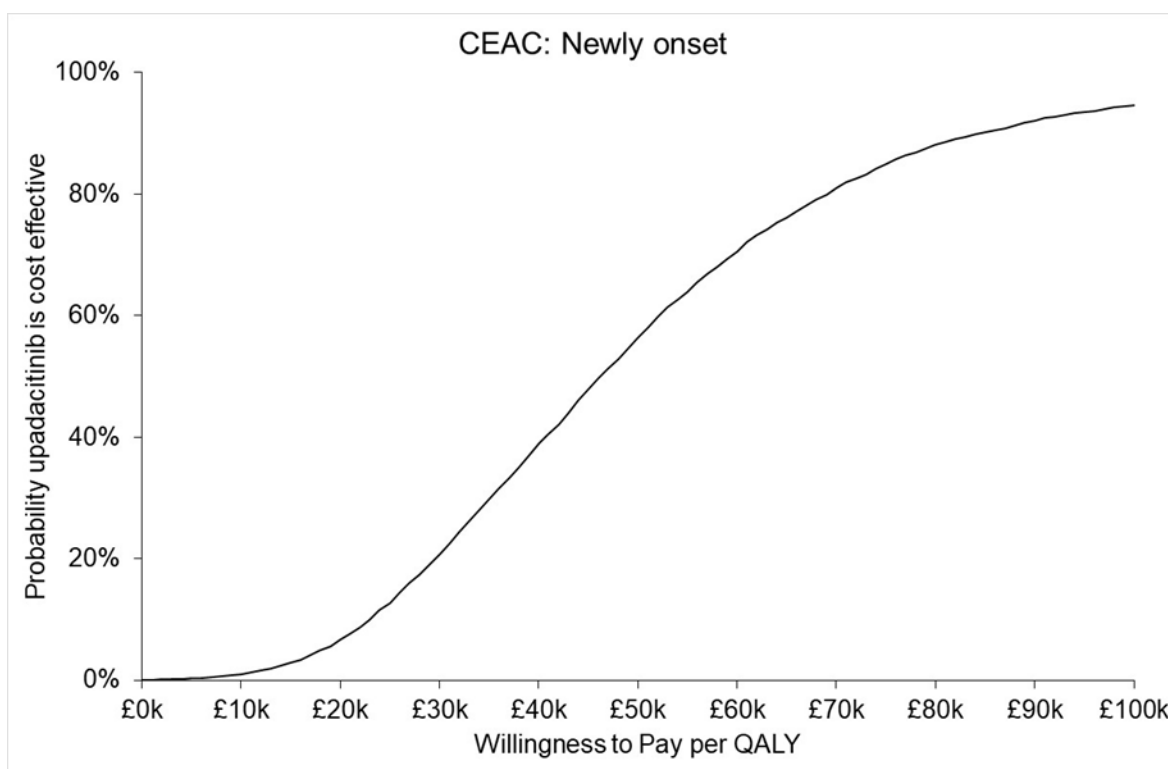


Figure 58: EAG base case: CEAC: new onset population

Probabilistic modelling results in a central estimate of £46,598 per QALY, and probabilities of being cost effective at willingness to pay values of £20,000, £30,000, £50,000 and £100,000 per QALY of 7%, 21%, 56% and 95% respectively.

5.6.1.3 EAG exploratory base case: relapsed subgroup

Costs and QALYs are summarised in Table 65 and Table 66.

Table 65: EAG base case: Costs: relapsed subgroup

	UPAD	PLAC	Net
Active treatment costs	████	████	████
Steroid costs	████	████	████
Pre-flare remission	████	████	████
Flare	████	████	████
Post-flare remission	████	████	████
GCA complications	████	████	████

GCE complications	■	■	■
JAK complications	■	■	■
Total	■	■	■

Table 66: EAG base case: QALYs: relapsed subgroup

	UPAD	PLAC	Net
Pre-flare remission	■	■	■
Flare	■	■	■
Post-flare remission	■	■	■
Main health states	■	■	■
GCA complications	■	■	■
GCE complications	■	■	■
JAK complications	■	■	■
Total	■	■	■

This results in the cost effectiveness estimates of Table 67.

Table 67: EAG base case: Summary: relapsed subgroup

	UPAD	PLAC	Net
Costs	■	■	■
QALYs	■	■	■
ICER			£98,754

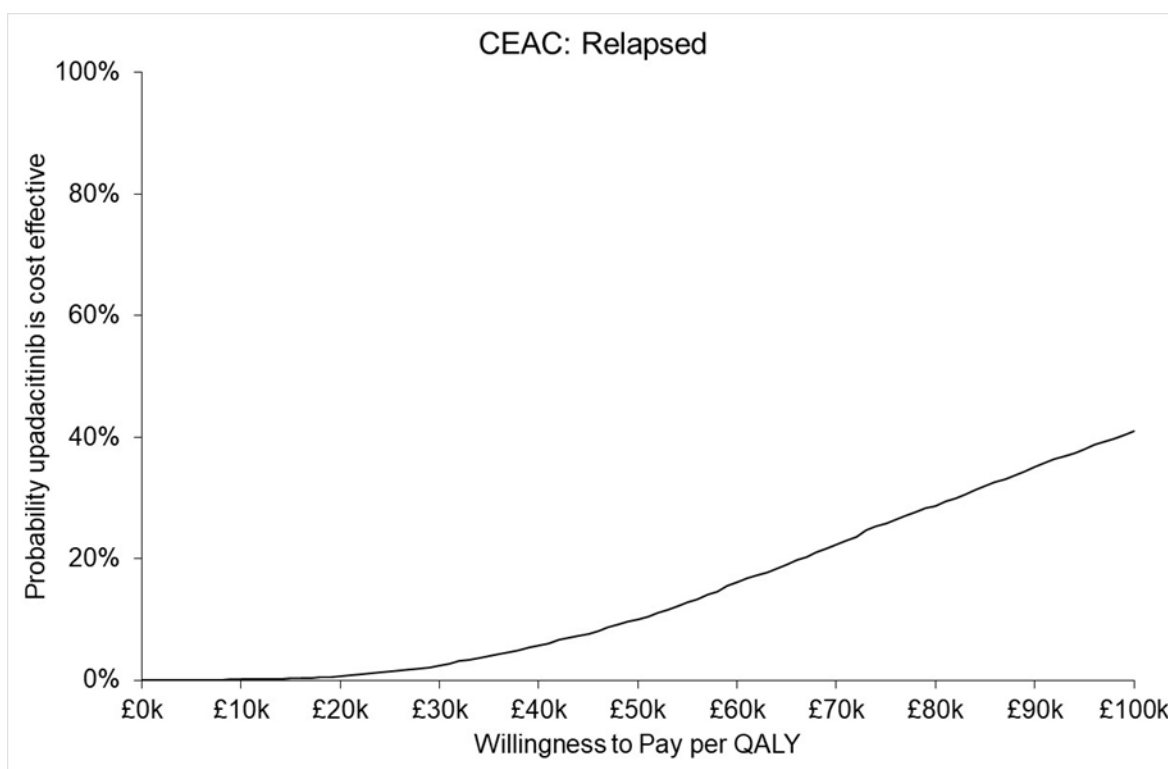


Figure 59: EAG base case: CEAC: relapsed subgroup

Probabilistic modelling results in a central estimate of £115,042 per QALY, and probabilities of being cost effective at willingness to pay values of £20,000, £30,000, £50,000 and £100,000 per QALY of 1%, 2%, 10% and 41% respectively.

5.6.2 EAG scenario analyses

The EAG presents the following scenario analyses⁷.

- SA01: Excluding the modelling of conditions the risks of developing which are affected by the total cumulative steroid dose to date.
- SA02: Assuming the subset of conditions identified in section 5.2.6 are determined by the total cumulative steroid dose in the previous year.
- SA03: Upadacitinib stopping rules of 1, 3 and 5 years
- SA04: Waning the time to first flare (TTFF) treatment effect from year three over 3, 5, 8 and 11 years

⁷ Note that the EAG scenario analyses retain the base case estimates of the mean steroid dose at baseline.

- SA05: Gompertz TTFF curves, also exploring treatment waning from year three over 3, 5, 8 and 11 years
- SA06: Generalised gamma TTFF curves, also exploring treatment waning from year three over 3, 5, 8 and 11 years
- SA07: Applying the patient group and arm specific lower and upper confidence bounds for the incidences of subsequent flares, and assuming a 20% annual incidence in both arms from end of year 2
- SA08: Quality of life values from simple averages of SELECT-GCA data, and from TA518
- SA09: Major stroke incidences that are 50% and 25% those of the company base case
- SA10: JAK related MACE events have the same cost as major stroke
- SA11: Halving monitoring costs
- SA12: Applying the median duration since diagnosis of ■ days rather than the mean duration since diagnosis of ■ days for those with relapsed disease when calculating the baseline total cumulative steroid dose to data.

Table 68: EAG scenario analyses

	ITT	New onset	Relapsed
EAG exploratory base case	£57,558	£42,918	£98,754
SA01: Exclude steroid complications	£131,703	£100,751	£241,553
SA02: Subset complications prev. year steroids	£99,103	£76,142	£211,139
SA03a: Upadacitinib stopping rule 1 year	£35,471	£21,213	£70,893
SA03b: Upadacitinib stopping rule 3 years	£74,825	£58,004	£109,002
SA03c: Upadacitinib stopping rule 5 years	£100,612	£79,198	£115,148
SA04a: Treatment waning over 3 years	£76,840	£62,017	£110,990
SA04b: Treatment waning over 5 years	£71,170	£57,296	£108,485
SA04c: Treatment waning over 8 years	£67,946	£53,275	£105,954
SA04d: Treatment waning over 11 years	£65,690	£51,009	£104,411
SA05a: Gompertz TTFF	£39,158	£13,468	£135,082
SA05b: Gompertz and waning over 3 years	£66,199	£47,094	£135,082

SA05c: Gompertz and waning over 5 years	£60,622	£40,535	£135,082
SA05d: Gompertz and waning over 8 years	£55,670	£33,291	£135,082
SA05f: Gompertz and waning over 11 years	£52,319	£28,559	£135,082
SA06a: Generalised gamma TTFF	£41,726	£28,056	£130,303
SA06b: Gen gamma and waning over 3 years	£68,532	£55,064	£130,303
SA06c: Gen gamma and waning over 5 years	£62,345	£49,434	£130,303
SA06d: Gen gamma and waning over 8 years	£56,936	£43,538	£130,303
SA06f: Gen gamma and waning over 11 years	£53,625	£39,935	£103,303
SA07a: Lower bound for secondary flares	£61,839	£46,853	£99,853
SA07b: Upper bound for secondary flares	£50,357	£35,887	£79,538
SA07c: 20% secondary flare annual incidence	£48,812	£40,661	£92,406
SA08a: SELECT-GCA average QoL	£58,023	£43,239	£95,689
SA08b: TA518 QoL	£55,447	£39,822	£99,651
SA09a: Major stroke 50% of base case	£60,972	£45,644	£104,399
SA09b: Major stroke 25% of base case	£62,848	£47,142	£107,512
SA10: JAK MACE same cost as major stroke	£61,184	£45,883	£104,619
SA11: Halving monitoring costs	£65,442	£50,582	£110,361
SA12: Median duration since diagnosis	£56,184	£42,918	£103,078

5.7 Conclusions of the cost effectiveness section

The EAG is concerned that the model may not be fit for purpose.

- The modelling of complications related to GCA flares typically relies upon incidence data around GCA diagnosis which may be too high for subsequent flares, or it relates to GCA in general rather than being specific to being in flare.
- The modelling of complications the risks of developing which are exacerbated by steroid use is questionable. There is a tension between the modelling of events the risks of which are best determined by the total cumulative steroid dose, this risk remaining elevated in perpetuity, and the modelling of events the risks of which are best determined by more recent steroid use such as the previous year's steroid use. For the latter patients might be best split into those not on steroids and those on steroids, these latter again being split into

risk bands of their previous year's steroid use. But this would still require credible risk estimates for each patient group.

- The EAG thinks that the risk estimates of steroid related events that the company derives from its US market survey lack face validity. The EAG is unclear whether the data of the US market survey could be reanalysed to provide more credible estimates.

The EAG thinks that the following SELECT-GCA data would be useful to Committee:

- The Period 2 Kaplan Meier data on time to first flare and time to subsequent flare separately by stratification, as requested under EAG clarification question A15.
- The upadacitinib arm Period 1 new incidences of steroid related complications, as requested under EAG clarification question A8.
- The new incidences of steroid related complications during Period 2 separately by stratification. The EAG did not request this data at clarification.
- The new incidences of GCA flare related complications, such as major stroke, during Period 1 separately for each arm and during Period 2 separately by stratification. The EAG did not request this data at clarification.

6 SEVERITY MODIFIERS

The company states that the QALY shortfalls are less than the severity modifier thresholds.

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<http://dx.doi.org/10.1002/art.40044>

8 APPENDICES

Appendix 1: EAG searches

Upadacitinib re-run search (without outcomes terms)

Carried out 19th July 2025

Ovid MEDLINE(R) ALL 1946 to July 29, 2025

- 1 giant cell arteritis.mp. or Giant Cell Arteritis/ or (giant adj2 cell adj2 arteritis).ti,ab,kw,ot,kf. 9865
- 2 (cranial arteritis or granulomatous arteritis or temporal arteritis or Horton's disease).ti,ab,kw,ot,kf. 2922
- 3 1 or 2 10288
- 4 (Upadacitinib or Rinvoq or ABT 494 or ABT494 or 1310726-60-3).ti,ab,kw,ot,kf. 1512
- 5 (Tocilizumab or Actemra or tocilizumab-bavi or Tofidence or Tyenne or RoActemra or Lusinex or TCZ or Atlizumab or MRA or MSB 11456 or MSB11456 or R 1569 or R1569 or RG 1569 or RG1569 or RHPM 1 or RHPM1 or RO 4877533 or RO4877533).ti,ab,kw,ot,kf. 18774
- 6 (Secukinumab or Cosentyx or AIN 457 or AIN457 or AIN 457A or AIN457A).ti,ab,kw,ot,kf. 2514
- 7 (Guselkumab or Tremfya or CNTO 1959 or CNTO1959).ti,ab,kw,ot,kf. 903
- 8 (steroid* or corticosteroid* or CS or prednisone or placebo).ti,ab,kw,ot,kf. 775513
- 9 4 or 5 or 6 or 7 or 8 795277
- 10 3 and 92323
- 11 limit 10 to humans 1991
- 12 limit 11 to (address or autobiography or bibliography or biography or classical article or comment or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or "expression of concern" or guideline or interactive tutorial or interview or lecture or legal case or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narrative or portrait or practice guideline or video-audio media or webcast) 112
- 13 11 not 12 1879
- 14 exp Randomized Controlled Trial/ 644827
- 15 exp Randomized Controlled Trials as Topic/ 189990
- 16 exp Clinical Trial/ 1029612
- 17 exp Random Allocation/ 108693
- 18 exp Double-Blind Method/ 185203
- 19 exp Single-Blind Method/ 35289
- 20 exp Clinical Trials as Topic/ 412144
- 21 (control* adj3 (study or studies or trial* or group*)).ti,ab,kw,ot,kf,pt. 1407322
- 22 ((random or randomi#ed) adj2 control* adj2 (trial* or study or studies)).ti,ab,kw,ot,kf,pt. 403065
- 23 ((Nonrandom* or non-random* or quasirandom* or quasi-random* or single arm or pragmatic or equivalence or open-label or noninferiority or non-inferiority) adj3 (trial* or study or studies)).ti,ab,kw,ot,kf,pt. 102559
- 24 (allocat* or double blind or single blind).ti,ab,kw,ot,kf,pt. 361479
- 25 (clinical adj2 (trial* or study or studies)).ti,ab,kw,ot,kf,pt. 817996
- 26 or/14-25 3053185

27 exp Observational Study/ 179738
 28 exp Case-Control Studies/ 1623439
 29 exp Cohort Studies/ 2774557
 30 observational.ti,ab,kw,ot,kf,pt. 334441
 31 ((observational or cohort or case control) adj3 (study or studies)).ti,ab,kw,ot,kf,pt.
 822720
 32 (prospective or retrospective).ti,ab,kw,ot,kf,pt. 1684276
 33 or/27-32 3814616
 34 Systematic review/ or meta analysis/ 326725
 35 (systematic review or systematic literature review or SLR or meta analys#s or
 NMA).ti,ab,kw,ot,kf,pt. 574234
 36 34 or 35 582252
 37 26 or 33 or 36 6349445
 38 13 and 37 683
 39 remission.ti,ab,kw,ot,kf. 156525
 40 ((corticosteroid* or steroid* or prednisone) adj4 (cumulative or expos* or
 dose)).ti,ab,kw,ot,kf. 24843
 41 (disease adj3 flare*).ti,ab,kw,ot,kf. 3115
 42 (36 item Short Form Quality of Life or SF 36 or SF36 or Physical Component Score
 or PCS).ti,ab,kw,ot,kf. 50157
 43 (Functional Assessment of Chronic Illness Therapy or FACIT).ti,ab,kw,ot,kf.
 2019
 44 (Treatment Satisfaction Questionnaire for Medication or TSQM).ti,ab,kw,ot,kf. 423
 45 (adverse event* or (adverse adj3 event*) or serious adverse event* or (serious adj3
 adverse adj3 event*)).ti,ab,kw,ot,kf. 312473
 46 withdrawal.ti,ab,kw,ot,kf. 113308
 47 (safety or efficacy or effectiveness).ti,ab,kw,ot,kf. 2382496
 48 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 2804009
 49 38 and 48 338
 50 10 and 37 784
 51 exp animals/ not humans.sh. 5361556
 52 50 not 51 783
 53 52 not 49 445

Embase <1974 to 2025 July 25>

1 giant cell arteritis.mp. or Giant Cell Arteritis/ or (giant adj2 cell adj2
 arteritis).ti,ab,kw,ot,kf. 13405
 2 (cranial arteritis or granulomatous arteritis or temporal arteritis or Horton's
 disease).ti,ab,kw,ot,kf. 3477
 3 1 or 2 15249
 4 exp upadacitinib/ or (Upadacitinib or Rinvoq or ABT 494 or ABT494 or 1310726-60-
 3).ti,ab,kw,ot,kf. 5047
 5 exp tocilizumab/ or (Tocilizumab or Actemra or tocilizumab-bavi or Tofidence or
 Tyenne or RoActemra or Lusinex or TCZ or Atlizumab or MRA or MSB 11456 or
 MSB11456 or R 1569 or R1569 or RG 1569 or RG1569 or RHPM 1 or RHPM1 or RO
 4877533 or RO4877533).ti,ab,kw,ot,kf. 54821
 6 exp secukinumab/ or (Secukinumab or Cosentyx or AIN 457 or AIN457 or AIN 457A
 or AIN457A).ti,ab,kw,ot,kf. 9937

7 exp guselkumab/ or (Guselkumab or Tremfya or CNTO 1959 or
 CNTO1959).ti,ab,kw,ot,kf. 3719
 8 exp corticosteroid therapy/ or exp corticosteroid/ or (corticosteroid* or steroid* or
 prednisone or CS or placebo).ti,ab,kw,ot,kf. 2123390
 9 4 or 5 or 6 or 7 or 8 2165332
 10 3 and 98180
 11 limit 10 to human 7728
 12 limit 11 to (books or chapter or editorial or letter or short survey) 813
 13 11 not 12 6915
 14 exp randomized controlled trial/ 1091984
 15 exp "randomized controlled trial (topic)"/ 297302
 16 exp randomization/ 101534
 17 exp equivalence trial/ 345
 18 exp non-inferiority trial/ 4024
 19 exp pragmatic trial/ 4277
 20 exp controlled study/ 11876801
 21 exp double blind procedure/ 306222
 22 single blind procedure/ 81384
 23 exp placebo/ 501010
 24 exp control group/ 109506
 25 (control* adj3 (study or studies or trial* or group*)).ti,ab,kw,ot,kf,pt. 2084260
 26 ((random or randomi#ed) adj2 control* adj2 (trial* or study or
 studies)).ti,ab,kw,ot,kf,pt. 598618
 27 ((Nonrandom* or non-random* or quasirandom* or quasi-random* or single arm or
 pragmatic or equivalence or open-label or noninferiority or non-inferiority) adj3 (trial* or
 study or studies)).ti,ab,kw,ot,kf,pt. 214153
 28 (allocat* or double blind or single blind).ti,ab,kw,ot,kf,pt. 560097
 29 (clinical adj2 (trial* or study or studies)).ti,ab,kw,ot,kf,pt. 1701735
 30 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
 or 29 13762609
 31 exp observational study/ or exp case control study/ or exp cohort analysis/ 1989594
 32 observational.ti,ab,kw,ot,kf,pt. 547945
 33 ((observational or cohort or case control) adj3 (study or studies)).ti,ab,kw,ot,kf,pt.
 1237972
 34 (prospective or retrospective).ti,ab,kw,ot,kf,pt. 2755159
 35 31 or 32 or 33 or 34 4170921
 36 "systematic review"/ or meta analysis/ 688370
 37 (systematic review or systematic literature review or SLR or meta analys#s or
 NMA).ti,ab,kw,ot,kf,pt. 665719
 38 36 or 37 840734
 39 13 and 30 2185
 40 13 and 35 1608
 41 13 and 38 [population and intervention and study types] 265
 42 exp remission/ 291939
 43 remission.ti,ab,kw,ot,kf. 278999
 44 ((corticosteroid* or steroid* or prednisone) adj4 (cumulative or expos* or
 dose)).ti,ab,kw,ot,kf. 49606
 45 (disease adj3 flare*).ti,ab,kw,ot,kf. 7190
 46 (36 item Short Form Quality of Life or SF 36 or SF36 or Physical Component Score
 or PCS).ti,ab,kw,ot,kf. 83763

47 (Functional Assessment of Chronic Illness Therapy or FACIT).ti,ab,kw,ot,kf.
5083

48 (Treatment Satisfaction Questionnaire for Medication or TSQM).ti,ab,kw,ot,kf.
1082

49 (adverse event* or (adverse adj3 event*) or serious adverse event* or (serious adj3
adverse adj3 event*)).ti,ab,kw,ot,kf. 570199

50 withdrawal.ti,ab,kw,ot,kf. 172800

51 (safety or efficacy or effectiveness).ti,ab,kw,ot,kf. 3562106

52 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 4342900

53 39 and 52 1087

54 40 and 52 745

55 41 and 52 133

56 53 or 54 or 55 1368

57 30 or 35 or 38 15938328

58 10 and 57 3080

59 (exp animal/ or exp invertebrate/ or nonhuman/ or animal experiment/ or animal
tissue/ or animal model/ or exp plant/ or exp fungus/) not (exp human/ or human tissue/)
8348271

60 58 not 59 3065

61 60 not 56 1697

Targeted search Upadacitinib

5th-6th June 2025

Systematic reviews/ meta-analyses

Ovid MEDLINE(R) ALL 1946 to June 05, 2025

1 Giant Cell Arteritis/ 8038

2 (giant adj2 cell adj2 arteritis).ti,ab,kf.6857

3 (cranial arteritis or granulomatous arteritis or temporal arteritis or Horton's disease or
large vessel vasculitis).ti,ab,kf. 4368

4 1 or 2 or 3 11019

5 (Upadacitinib or Rinvoq or ABT 494 or ABT494 or 1310726-60-3).af. 1466

6 (Tocilizumab or Actemra or tocilizumab-bavi or Tofidence or Tyenne or RoActemra
or Lusinex or TCZ or Atlizumab or MRA or MSB 11456 or MSB11456 or R 1569 or R1569
or RG 1569 or RG1569 or RHPM 1 or RHPM1 or RO 4877533 or RO4877533).af.
19401

7 (Secukinumab or Cosentyx or AIN 457 or AIN457 or AIN 457A or AIN457A).af.
2585

8 (Guselkumab or Tremfya or CNTO 1959 or CNTO1959).af. 914

9 Methotrexate/ 42925

10 (Methotrexate or amethopterin or mexate).af. 64385

11 or/5-1086965

12 "Systematic Review"/ 295113

13 (systematic review or meta-analysis).pt. 382220

14 meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis
as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology
assessment, biomedical/ or network meta-analysis/ 428049

15 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or
overview*))).ti,ab,kf. 420953

- 16 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf. 14221
- 17 (meta regression* or metaregression*).ti,ab,kf. 18745
- 18 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. 580249
- 19 ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf. 5047
- 20 (mixed adj3 treatment adj3 (meta-analy* or metaanaly*).ti,ab,kf. 186
- 21 review.ti. 849908
- 22 or/12-21 1134682
- 23 4 and 11 and 22 93

Embase 1974 to 2025 June 04

- 1 exp giant cell arteritis/15211
- 2 (giant adj2 cell adj2 arteritis).ti,ab,kf.10570
- 3 (cranial arteritis or granulomatous arteritis or temporal arteritis or Horton's disease or large vessel vasculitis).ti,ab,kf. 6328
- 4 or/1-3 17716
- 5 upadacitinib/ 4590
- 6 (Upadacitinib or Rinvoq or ABT 494 or ABT494 or 1310726-60-3).ti,ab,kf. 3032
- 7 (Tocilizumab or Actemra or tocilizumab-bavi or Tofidence or Tyenne or RoActemra or Lusinex or TCZ or Atlizumab or MRA or MSB 11456 or MSB11456 or R 1569 or R1569 or RG 1569 or RG1569 or RHPM 1 or RHPM1 or RO 4877533 or RO4877533).ti,ab,kf. 36262
- 8 tocilizumab/ 33016
- 9 secukinumab/ 9392
- 10 (Secukinumab or Cosentyx or AIN 457 or AIN457 or AIN 457A or AIN457A).tw,kf. 5458
- 11 guselkumab/ 3462
- 12 (Guselkumab or Tremfya or CNTO 1959 or CNTO1959).tw,kf. 1948
- 13 methotrexate/ 230594
- 14 (Methotrexate or amethopterin or mexate).tw,kf. 90304
- 15 or/5-14291837
- 16 4 and 15 3154
- 17 "systematic review"/ 530408
- 18 meta analysis/ 359955
- 19 biomedical technology assessment/ 19473
- 20 network meta-analysis/ 10963
- 21 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf. 502215
- 22 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf. 24353
- 23 (meta regression* or metaregression*).ti,ab,kf. 22510
- 24 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. 897090
- 25 ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf. 8802
- 26 (mixed adj3 treatment adj3 (meta-analy* or metaanaly*).ti,ab,kf. 266

27	or/17-26	937290
28	16 and 27	198

Epistemonikos

Title/ abstract: (title:("giant cell arteritis") OR abstract:("giant cell arteritis")) AND (title:(upadacitinib) OR abstract:(upadacitinib)) limited to systematic reviews 2 results

(title:(Tocilizumab) OR abstract:(Tocilizumab)) AND (title:("giant cell arteritis") OR abstract:("giant cell arteritis")) limited to systematic reviews 28 results

(title:((title:(secukinumab) OR abstract:(secukinumab)) AND (title:("giant cell arteritis") OR abstract:("giant cell arteritis")))) OR abstract:((title:(secukinumab) OR abstract:(secukinumab)) AND (title:("giant cell arteritis") OR abstract:("giant cell arteritis")))) 0 results

(title:(guselkumab) OR abstract:(guselkumab)) AND (title:("giant cell arteritis") OR abstract:("giant cell arteritis")) 0 results

(title:(methotrexate) OR abstract:(methotrexate)) AND (title:("giant cell arteritis") OR abstract:("giant cell arteritis")) limit to systematic reviews 23 results

Cochrane library

ID	Search Hits
#1	MeSH descriptor: [Giant Cell Arteritis] this term only 160
#2	(giant NEAR/2 cell NEAR/2 arteritis):TI,AB,KW 369
#3	("cranial arteritis" or "granulomatous arteritis" or "temporal arteritis" or "Horton's disease" or "large vessel vasculitis"):ti,ab,kw85
#4	#1 or #2 or #3 401

Limit to CDSRs 3 results

INAHTA

Giant cell arteritis 3 results

Longitudinal/ Natural history/ baseline events

Ovid MEDLINE(R) ALL 1946 to June 05, 2025

Ovid MEDLINE(R) ALL <1946 to June 05, 2025>

1	Giant Cell Arteritis/	8038
2	(giant adj2 cell adj2 arteritis).ti,ab,kf.	6857
3	(cranial arteritis or granulomatous arteritis or temporal arteritis or Horton's disease or large vessel vasculitis).ti,ab,kf.	4368
4	1 or 2 or 3	11019
5	(Upadacitinib or Rinvoq or ABT 494 or ABT494 or 1310726-60-3).af.	1466
6	(Tocilizumab or Actemra or tocilizumab-bavi or Tofidence or Tyenne or RoActemra or Lusinex or TCZ or Atlizumab or MRA or MSB 11456 or MSB11456 or R 1569 or R1569	

or RG 1569 or RG1569 or RHPM 1 or RHPM1 or RO 4877533 or RO4877533).af.
19401
7 (Secukinumab or Cosentyx or AIN 457 or AIN457 or AIN 457A or AIN457A).af.
2585
8 (Guselkumab or Tremfya or CNTO 1959 or CNTO1959).af. 914
9 Methotrexate/ 42925
10 (Methotrexate or amethopterin or mexate).af. 64385
11 or/5-1086965
12 exp epidemiologic studies/ 3483589
13 (frequency or frequencies or occurrence\$ or incidence\$ or prevalence\$ or number\$ or
times or rate or rates or episode\$ or natural history).ti,ab. 9038004
14 Longitudinal Studies/ 185285
15 Epidemiological Models/ 541
16 (epidemiological* adj3 (study* or data or research or model*)).tw,kf. 63308
17 (Baseline adj1 (event* or risk*)).tw,kf. 4460
18 exp data collection/ 2732379
19 (Observational Study or Validation Studies or Clinical Study).pt. 184159
20 (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
276223
21 (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
607478
22 ((follow up or followup) adj7 (study or studies or design or analysis or
analyses)).ti,ab,kf. 192047
23 ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or
analysis or analyses or data)).ti,ab,kf. 405959
24 (retrospective adj7 (study or studies or design or analysis or analyses or data or
review)).ti,ab,kf. 835649
25 (population adj3 (study or studies or analysis or analyses)).ti,ab,kf. 267636
26 ((multidimensional or multicentre or multicenter or (multi adj dimensional)) adj3
(study or studies or design or analysis or analyses)).ti,ab,kf. 134155
27 (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf. 58475
28 Recurrence/ 206850
29 or/12-28 12404092
30 4 and 11 and 29 415

Embase 1974 to 2025 June 04

1 exp giant cell arteritis/15211
2 (giant adj2 cell adj2 arteritis).ti,ab,kf. 10570
3 (cranial arteritis or granulomatous arteritis or temporal arteritis or Horton's disease or
large vessel vasculitis).ti,ab,kf. 6328
4 1 or 2 or 3 17716
5 upadacitinib/ 4590
6 (Upadacitinib or Rinvoq or ABT 494 or ABT494 or 1310726-60-3).ti,ab,kf.
3032
7 tocilizumab/ 33016
8 (Tocilizumab or Actemra or tocilizumab-bavi or Tofidence or Tyenne or RoActemra
or Lusinex or TCZ or Atlizumab or MRA or MSB 11456 or MSB11456 or R 1569 or R1569
or RG 1569 or RG1569 or RHPM 1 or RHPM1 or RO 4877533 or RO4877533).ti,ab,kf.
36262

9 secukinumab/ 9392
 10 (Secukinumab or Cosentyx or AIN 457 or AIN457 or AIN 457A or AIN457A).tw,kf.
 5458
 11 guselkumab/ 3462
 12 (Guselkumab or Tremfya or CNTO 1959 or CNTO1959).tw,kf. 1948
 13 methotrexate/ 230594
 14 (Methotrexate or amethopterin or mexate).tw,kf. 90304
 15 or/5-14291837
 16 4 and 15 3154
 17 longitudinal study/ 244351
 18 (longitudinal adj1 stud*).tw,kf. 154438
 19 epidemiological model/ 1159
 20 (epidemiological* adj3 (study* or data or research or model*)).tw,kf. 85796
 21 (Baseline adj1 (event* or risk*)).tw,kf. 7711
 22 (times or rate or rates).ti,kf. 434280
 23 (frequency or frequencies or occurrence\$ or incidence\$ or prevalence\$ or number\$ or
 natural history or episode*).tw,kf. 7973936
 24 or/17-23 8521083
 25 16 and 24 753

Standard mortality ratios

Ovid MEDLINE(R) ALL 1946 to June 05, 2025

1 Giant Cell Arteritis/ 8038
 2 (giant adj2 cell adj2 arteritis).ti,ab,kf.6857
 3 (cranial arteritis or granulomatous arteritis or temporal arteritis or Horton's disease or
 large vessel vasculitis).ti,ab,kf. 4368
 4 1 or 2 or 3 11019
 5 standard mortality ratio*.tw,kf. 228
 6 "Cause of Death"/ 56678
 7 mortality/ or survival rate/ 246288
 8 4 and 731

Embase 1974 to 2025 June 06

1 exp giant cell arteritis/15172
 2 (giant adj2 cell adj2 arteritis).ti,ab,kf.10555
 3 (cranial arteritis or granulomatous arteritis or temporal arteritis or Horton's disease or
 large vessel vasculitis).ti,ab,kf. 6301
 4 1 or 2 or 3 17672
 5 mortality rate/ 175683
 6 *mortality/ 129611
 7 standard mortality ratio*.tw,kf. 302
 8 *"cause of death"/ 14292
 9 survival rate/ 345387
 10 or/5-9 631893
 11 4 and 10 238

Ovid MEDLINE(R) ALL 1946 to June 06, 2025

- 1 Giant Cell Arteritis/ 8041
- 2 (giant adj2 cell adj2 arteritis).ti,ab,kf.6859
- 3 (cranial arteritis or granulomatous arteritis or temporal arteritis or Horton's disease or large vessel vasculitis).ti,ab,kf. 4369
- 4 1 or 2 or 3 11021
- 5 Drug Tapering/ 558
- 6 exp Adrenal Cortex Hormones/ 437288
- 7 Placebo Effect/ 5354
- 8 6 or 7 442545
- 9 5 and 870
- 10 ((corticosteroid* or course* or steroid* or placebo* or pbo) adj3 taper*).tw,kf. 2656
- 11 9 or 10 2714
- 12 Real world.tw,kf. 116796
- 13 Meta-Analysis as Topic/ 26362
- 14 Network Meta-Analysis/ 7426
- 15 meta-analysis.pt. 217684
- 16 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf. 14225
- 17 (meta regression* or metaregression*).ti,ab,kf. 18762
- 18 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. 580848
- 19 ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf. 5051
- 20 (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf. 186
- 21 or/12-20 706648
- 22 4 and 11 and 21 4

Embase 1974 to 2025 June 06

- 1 exp giant cell arteritis/15172
- 2 (giant adj2 cell adj2 arteritis).ti,ab,kf.10555
- 3 (cranial arteritis or granulomatous arteritis or temporal arteritis or Horton's disease or large vessel vasculitis).ti,ab,kf. 6301
- 4 1 or 2 or 3 17672
- 5 drug dose reduction/ 111101
- 6 exp corticosteroid/ or steroid hormone/ 1252079
- 7 placebo/ 495415
- 8 6 or 7 1699368
- 9 5 and 852947
- 10 ((corticosteroid* or course* or steroid* or placebo* or pbo) adj3 taper*).tw,kf. 7741
- 11 9 or 10 59858
- 12 4 and 11 893
- 13 real world.af. 196922
- 14 exp evidence based medicine/ or statistical analysis/ 2462566
- 15 meta analysis/ or network meta-analysis/ 362733
- 16 meta-analysis.pt. 0

17 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf. 24409

18 (meta regression* or metaregression*).ti,ab,kf. 22521

19 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. 898493

20 ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf. 8808

21 (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf. 267

22 or/13-21 2850004

23 12 and 22 123

Appendix 2: Further information on risk of bias assessment

Table 69: ROBINS assessment

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes	The CS clearly states that the review was conducted to identify evidence of the efficacy and safety of interventions used to treat GCA. However, there is no explicit report of predefined protocol.
1.2 Were the eligibility criteria appropriate for the review question?	Probably yes	The company have used two different PICOS criteria reported in CS Appendix B, Table 11 and Table 12. The EAG identified restrictions in the PICOS criteria reported in CS Appendix B, Table 12.
1.3 Were eligibility criteria unambiguous?	Yes	Eligibility criteria were clear.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably yes	Restrictions were generally appropriate; however, no justification was provided for limitations on study design and outcomes. These were likely appropriate restrictions.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Yes	No language or time restrictions were included.
Concerns regarding specification of study eligibility criteria	Low concern	Overall, the EAG agrees with the eligibility criteria.
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of databases/ electronic	Probably yes	Search included eight databases, and additional supplementary search was

sources for published and unpublished reports?		performed. However, no unpublished literature was searched.
2.2 Were methods additional to database searching used to identify relevant reports?	Yes	Two conference proceedings and six clinical trial registries were searched
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably no	The EAG raises concerns regarding search terms and overall search strategy and anticipates that potentially relevant studies may have excluded.
2.4 Were restrictions based on date, publication format, or language appropriate?	Probably yes	No language restrictions we applied. However, focused PICOS criteria is restricted to RCTs only.
2.5 Were efforts made to minimise errors in selection of studies?	Yes	Two reviewers independently screened all abstracts and full texts, and any discrepancies were resolved by a third reviewer.
Concerns regarding methods used to identify and/or select studies	Some concerns	Overall, the EAG agrees with the process of study selection. However, raised concerns regarding the search strategy.
3: Data collection and study appraisal sections		
3.1 Were efforts made to minimise error in data collection?	Yes	Standardised form used, extraction by two reviewers for the final list of included studies and a third reviewer to reach consensus for any remaining discrepancies
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes	Comprehensive description of study characteristics for RCTs and observational studies were reported in CS Appendix B, Table 14 to Table 16 and CS Appendix B, Table 25 to Table 26
3.3 Were all relevant study results collected for use in the synthesis?	Probably yes	Only one trial (SELECT-GCA) was selected after conducting the SLR. The other studies were not included to perform indirect treatment comparison.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes	The risk of bias assessment was done using the recommended Cochrane risk of bias tool for randomised trials and observational studies. However, a narrative of the ratings was not provided. The EAG separately evaluated ROB and rated the RCTs as low risk of bias.
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes	The risk of bias was evaluated using suitable criteria, with assessment conducted by two reviewers.

Concerns regarding methods used to collect data and appraise studies	Low concern	The EAG agrees with company's approach to conduct data extraction and quality appraisal.
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	Probably no	The company only selected one trial as clinical evidence. No additional analysis was performed
4.2 Were all predefined analyses followed or departures explained?	No information	There were no pre-defined analyses plan reported in CS Appendix B.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Probably no	The company identified only one eligible RCT to inform the clinical evidence and no indirect treatment comparisons were conducted even though relevant comparator was identified
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Not applicable	The company identified only one eligible RCT to inform the clinical evidence
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Not applicable	The company identified only one eligible RCT to inform the clinical evidence
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Yes	Although risk of bias assessment was not included to interpret the synthesis. However, the included studies were assessed as 'low risk of bias'
Concerns regarding the synthesis and findings	Some concern	Overall, the EAG raises concerns regarding omission of indirect comparison
Risk of bias		
A. Did the interpretation of findings address all of the concerns identified in the Phase 2 assessment?	Unclear concern	There is a reasonable concern regarding identification of relevant studies, which might limit further analysis.
B. Was the relevance of identified studies to the review's research question appropriately considered?	Yes	The included studies were relevant to the review's research question.
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Unclear concerns	The company included only one eligible RCT to inform the clinical evidence and no indirect analysis were conducted even though relevant treatment comparator was identified

Table 70: Risk of bias assessment of randomised controlled trials using revised Cochrane risk of bias tool (RoB2)

Checklist questions	SELECT-GCA (NCT03725202) Abbvie (2024) ^{85, 86}	EAG assessment	GiACTA (NCT01791153) Stone (2017) ⁶⁴	EAG assessment	TitAIN (NCT03765788) Venhoff (2023) ⁸⁷	EAG assessment	ABA (NCT00556439) Langford (2017) ⁸⁸	EAG assessment
1. Randomization								
1.1 Was the allocation sequence random?	Y	Y	Y	Y	Y	Y	Y	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	Y	Y	PY	Y	Y	Y	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	N	N	PN	PN	N	N

Risk of bias judgement	Low	Low	Low	Low	Low	Low	Low	Low
2. Deviations from intended interventions								
2.1 Were participants aware of their assigned intervention during the trial?	N	N	N	N	N	N	N	N
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	N	N	N	N	N	N	N
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable

experimental context?								
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Y	Y	Y	PN	PN	Y	Y
Risk of bias judgement	Low	Low	Low	Low	Low	Low	Low	Low
3. Missing outcome data								
3.1 Were data for this outcome	Y	Y	Y	Y	Y	Y	Y	Y

available for all, or nearly all, participants randomized?

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable

3.3 If N/PN to 3.2: Could missingness in the outcome	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable

3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable

Risk of bias judgement	Low	Low	Low	Low	Low	Low	Low	Low

4. Measurement of the outcome

4.1 Was the method of measuring the outcome inappropriate?	N	N	N	N	N	PN	PN	N

4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	PN	N	PN	N	PN	N	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N	N	N	N	N	PY	PN	PN
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	N	Not Applicable	Not Applicable
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable

of intervention
received?

Risk of bias
judgement

Low

Low

Low

Low

Low

Low

Low

Low

5. Selection of
the reported
result

5.1 Were the
data that
produced this
result
analysed in
accordance
with a pre-
specified
analysis plan
that was
finalized
before
unblinded
outcome data
were available
for analysis?

Y

Y

Y

Y

Y

Y

Y

Y

5.2 Is the
numerical
result being
assessed
likely to have
been selected,
on the basis of
the results,
from multiple
eligible

N

N

N

N

N

N

PN

N

outcome
measurements
(e.g. scales,
definitions,
time points)
within the
outcome
domain?

5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N	N	PN	PN	N	N	PN	PN
Risk of bias judgement	Low	Low	Low	Low	Low	Low	Low	Low
Overall	Low	Low	Low	Low	Low	Low	Low	Low
Overall bias	Low	Low	Low	Low	Low	Low	Low	Low

Appendix 3: Full list of conditions exacerbated by steroid use: SELECT-GCA versus company market survey and mode

The full list of conditions exacerbated by steroid use is presented in Table 71.

Table 71: Full set of conditions exacerbated by steroid use: SELECT-GCA vs company market survey

SELECT-GCA placebo arm		Company market survey		Ratio
Blood (Na/K) decreased	████	Electrolytes (Na/K) abnormalities*	████	████
Cardiac failure	████	Hospitalization with heart failure	████	████
Palpitations	████	Palpitations*	████	████
Tendon disorder	████	Tendon rupture*	████	████
All fractures	████	Non-traumatic fracture*	████	████
GI perforation	████	GI perforation*	████	████
Ulcers	████	Ulcer/GI bleed*	████	████
Gastritis	████	Gastritis*	████	████
Mental health	████	Mental health**	████	████
..	████	Opportunistic infections*	████	████
Sepsis	████	Sepsis*	████	████
Serious infections	████	Severe infection: Hospitalizations	████	████
Cataract	████	Diagnosed cataract*	████	████
IOP increased	████	Increased IOP*	████	████
Sleep disorders	████	Sleep disorders**	████	████
Dyspnoea	████	Dyspnoea*	████	████
Increased tendency to bruise	████	Bruising*	████	████
Skin thinning	████	Skin thinning*	████	████
Impaired wound healing	████	Impaired wound healing*	████	████
Acne	████	Acne*	████	████
Hirsutism	████	Hirsutism*	████	████
Weight increase	████	Increased BMI	████	████
Steroid diabetes	████	Pre-diabetes*	████	████
Type 2 diabetes mellitus	████	Type 2 diabetes*	████	████
Hyperlipidaemia	████	Hyperlipidaemia**	████	████

Adrenal suppression	■	Endocrine adrenal insufficiency*	■	■
Cushing's syndrome	■	Cushing's syndrome**	■	■
Myopathy	■	Myopathy*	■	■
..	■	Aseptic necrosis of bone*	■	■
Hypertension	■	Hypertension**	■	■
Arterioscl. coronary artery	■	Atherosclerosis**	■	■
Osteoporosis	■	Osteoporosis**	■	■
Glaucoma	■	Glaucoma**	■	■
* Newly diagnosed, ** Newly diagnosed and treated, Mental health: Pooled anxiety, depression, mania, psychosis and delirium				

Single Technology Appraisal

Upadacitinib for treating giant cell arteritis [ID6299]

EAG report – factual accuracy check and confidential information check

'Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.' (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 8 August 2025** using the below 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 committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Tocilizumab was not included as a comparator

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report repeatedly states that <i>'tocilizumab was not included as a comparator'</i> in the company submission (e.g. pages 13, 15, 18, 33, 34, 39, 88, 145 and 115 and Tables 1 and 5) which importantly removes the context and mischaracterizes the company's position.	The company suggests replacing and/or amending all instances of <i>'was not included as a comparator'</i> with language clarifying that tocilizumab: <i>'was not considered a relevant comparator in the company's base-case submission'</i>.	To avoid mischaracterising the company's position and to avoid falsely depicting the intentionality behind not considering tocilizumab as a relevant comparator.	Not a factual inaccuracy. Tocilizumab was included neither in the base-case nor in any of the scenario and subgroup analyses provided by the company.

Page 19 - The EAG report highlights the possibility of scenario analyses incorporating tocilizumab both downstream of new-onset treatment and for relapsing GCA, which can be perceived as prematurely drawing conclusions: <i>‘As tocilizumab was considered cost-effective in patients with relapsing GCA based on TA518, inclusion of tocilizumab in the modelled treatment pathway is likely to reduce the incremental QALY gain for upadacitinib compared with comparator (standard care) for patients with new on-set GCA’.</i>	The company suggests removing the text as this statement is not related to Key Issue 1. Key Issue 1 focuses on the inclusion of a comparator in a subpopulation whereas this statement refers to a highly uncertain assessment of treatment sequencing yielding speculative results in the new-onset population.	To ensure the commentary in the report accurately reflects and supports the related issue, AbbVie requests commentary regarding speculative and uncertain results regarding treatment sequencing are removed to avoid factually inaccurate conclusions to be drawn.	Not a factual inaccuracy. As no analysis which took into account the use of tocilizumab in the treatment pathway was provided by the company, the EAG described the likely impact of incorporating tocilizumab on cost-effectiveness analysis in the best interest of the NICE committee. EAG’s statement was based on simple reasoning and was not highly uncertain.
Page 19 – The EAG report further speculates that TA518 found tocilizumab cost-effective at £24,977/QALY and suggests that its inclusion would likely	The company suggests amendments are made to the following text on page 19 of the EAG report: <i>‘the potential difference in effectiveness in favour of tocilizumab cannot be ruled out</i>	It would be factually inaccurate and misleading to base a conclusion of a technology’s ICER vs an alternative technology based on ICER stated in the	Not a factual inaccuracy. The EAG had taken care in its wording to reflect uncertainty and the statement was based

reduce the incremental QALY gain for upadacitinib, while prematurely assuming that a potential efficacy advantage for tocilizumab 'cannot be ruled out'.	<i>based on the EAG's preliminary adjusted indirect comparison (see also Key issue 3). The effect on ICER is unknown. But it can be noted that TA518 estimated tocilizumab to have an ICER of £24,977 per QALY among relapsed patients which is less than both the EAG corrected company base case estimate of £38,359 per QALY and the EAG exploratory base case of £57,588 per QALY for upadacitinib compared to placebo.'</i> Requested amendment: <i>'the impact on upadacitinib's ICER against tocilizumab remains unknown without head-to-head or robust indirect comparison data' .</i>	alternative technologies previous NICE appraisal. This would not be directly comparable due to differences in methodology and assumptions	on the best available evidence assembled by the EAG in the absence of any alternative analysis provided by the company. It is not speculation that TA518 found tocilizumab to be cost effective at £24,977/QALY. A QALY gain was modelled for tocilizumab over placebo so if tocilizumab was considered as a comparator the total QALYs for tocilizumab would probably (inevitably) be greater than those of placebo so the incremental QALY gain for upadacitinib compared to tocilizumab will be less than for

			upadacitinib compared to placebo.
Page 13, 18, 33, 34, and Table 1 – The EAG report critically omits the tocilizumab stopping rule <i>‘tocilizumab was recommended for people with refractory/relapsing GCA in NICE TA518’</i>	AbbVie suggests revising the following text: <i>‘tocilizumab was recommended for people with refractory/relapsing GCA in NICE TA518’</i> The text should include reference to tocilizumab’s fixed one-year stopping rule as follows: ‘tocilizumab was recommended for people with refractory/relapsing GCA in NICE TA518 subject to a fixed one-year stopping rule’	To accurately reflect NICE’s recommendation on the use of tocilizumab in patients with GCA. This is required to provide the Committee with the critical context when considering the Company’s positioning of upadacitinib and comparator selection.	Not a factual inaccuracy. But the EAG accepts the company proposed amendment.

Issue 2 No clinical effectiveness data beyond year 1 from the pivotal trial, SELECT-GCA, were presented

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 13, 20, 88, 155, and 187 – The language in the EAG report regarding the	AbbVie request that the EAG report is amended to reflect that the company	The current wording risks misrepresentation. It implies that AbbVie may have	No factual error. The EAG report is clear that formal

absence of clinical effectiveness data beyond year 1 omits crucial context regarding why period 2 data was not provided to the EAG at the time of CQ.	did provide context in its response to Clarification Question A15: <i>‘that the Period 2 cohort comprises patients who had already achieved at least 24 weeks of remission and were thus a pre-selected, sustained-response population, making the requested data unrepresentative for extrapolation in the economic model’.</i> Furthermore, AbbVie suggest clearly articulating that these data are not yet available.	withheld or dismissed additional data without justification. It is important to add that the period 2 data is still not available and topline data will be available in due course.	incorporation of Period 2 data into the current model structure would be difficult but that it thinks that Period 2 data would still be useful to Committee. The EAG has added “Phase 2 of the trial was completed in March 2025. The company stated during FAC that this Phase 2 data is still not available but that topline data will be available in due course. It does not specify when.”
Page 14, 20, 111, 113, 115, 116, 118, 155, 162, 184, and Table 68 – The EAG report repeatedly refers to a ‘two year stopping rule’ which conflates the company’s base case modelling assumption with an actual recommendation of a stopping rule.	AbbVie requests to remove all references to a stopping rule for Upadacitinib. The company presented base case treatment durations, and not stopping rules. AbbVie suggest rewording the ‘two year stopping rule’ to: <i>‘A two-year treatment duration was assumed for its base case’</i>	AbbVie considers the statements to be factually incorrect; the company’s base case models a two-year treatment duration as a scenario, and it is important not to confuse this with a stopping rule.	This raises a major issue of relevance of the economic modelling compared to the position sought. The EAG has added an additional issue for this: what is the relevance of the economic modelling to the position sought,

		As described in the CS, treatment duration for GCA should be guided by disease activity, clinician judgement, and patient choice. The treatment duration for upadacitinib in the base case is 2 years. A variety of scenario analysis evaluating the cost-effectiveness of different treatment durations were included in the submission to position upadacitinib as a flexible and long-term corticosteroid-sparing treatment option. As both the CS and EAG report state, <i>'there remains a significant unmet need for long-term, effective, and well-tolerated corticosteroid-sparing treatments'</i>. A stopping rule would prevent Upadacitinib providing such a flexible treatment for patients and should be avoided.	should there be a stopping rule and if so what length should it be. The EAG has also added a section at the start of 5.1 to cover this.

Issue 3 Difference in clinical effectiveness between upadacitinib and tocilizumab cannot be ruled out

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In issue 3, the EAG report includes a preliminary adjusted indirect comparison between upadacitinib and tocilizumab with the report stating that it: <i>‘indicated some possibility of difference in clinical effectiveness in favour of tocilizumab’</i>. This statement could be misleading as it does not specify the methodology followed and the uncertainty of these results is not accounted for. Furthermore, the report states <i>‘the company could undertake adjusted indirect comparison to provide estimates for relative effectiveness for upadacitinib compared with tocilizumab’</i>	AbbVie recommend revising the text to specify which type of adjusted indirect comparison was performed and AbbVie suggest reframing the following sentence: <i>‘the company could undertake adjusted indirect comparison ... which could then be incorporated into its economic modelling’</i> With language to the effect of: <i>‘an adjusted indirect comparison could be performed to generate point estimates, but these would be associated with unquantifiable uncertainties due to the heterogeneity in the trial design and patient populations, limiting the value of the analysis for decision-making.’</i>	It is not appropriate to frame tocilizumab’s efficacy as more favourable with the preliminary ITC results without acknowledging the high level of uncertainty and no further details on how the analysis was performed. In reality, heterogeneity across trial design and population mean any indirect estimate would carry wide confidence intervals and uncertain validity.	No factual error. The EAG has now referenced the methodology used for the adjusted indirect comparison in Section 2.5.2 and provided the reference: Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997 Jun;50(6):683-91. doi: 10.1016/s0895-4356(97)00049-8. The EAG clearly acknowledged the limited statistical power in relation to relatively small sample sizes of

<i>for patients with relapse/refractory disease’.</i> Notwithstanding the position that tocilizumab is not a relevant comparator, this statement could be misleading as it does not highlight the shortcomings of the approach due to fundamental differences between the trials that would result in unquantifiable uncertainties.			the trials and the inability to adjust for some potential differences in prognostic factors between trial participants in the adjusted indirect comparison, and had taken care in its wording to account for the uncertainty associated with the heterogeneity in trial population.
The EAG report suggests <i>‘major model revisions to permit the sequencing of treatments to be explored’</i> as an additional evidence recommendation for resolving issue 3. However, it is misleading to include treatment sequencing as a solution to this issue.	The company suggest limiting the additional evidence recommendation to conducting an ITC only, as proposing major model restructuring or treatment sequencing is not aligned to the issue identified.	It is inaccurate to mention that modelling treatment sequencing in the model will help assess the relative effectiveness of tocilizumab versus upadacitinib. Treatment sequencing is discussed in issue 5 and this commentary leads to the conflation of two separate issues, misleading the reader.	No factual error. No revision needed. These are separate issues: (A) comparing upadacitinib with tocilizumab among the relapsed, (B) considering treatment sequencing among the new onset such that when relapsed they may receive tocilizumab (or

			upadacitinib if they have not previously received it.
Section 2.5.1.6 In the EAG report, the SELECT-GCA Upadacitinib and placebo arms (52-week taper) are compared with a pooled GiACTA KM curve that combines 26- and 52-week placebo taper groups and two tocilizumab dosing regimens which is not appropriate. By using the pooled GiACTA estimates (~36% flare-free at one year), it makes the SELECT-GCA curve (~50% flare-free at one year) appear unusually favourable, then labels any continuation of that gap beyond one year as '<i>unknown</i>' and attributable only to '<i>poor [model] fit</i>'.	It would be more methodologically appropriate and robust for the EAG to restrict this comparison to the 52-week taper arm and to the licensed dose of tocilizumab for GCA or suggest contextualising the text to acknowledge the impact of pooling the GiACTA placebo arms and the two tocilizumab arms. The company suggests the following points are included a) A 26-week taper is not reflective of clinical practice and is more aggressive tapering and therefore, the pooled placebo arm shows worse results than the 52-week taper b) This comparison does not represent a head-to-head match with the SELECT-GCA 52-week taper	Comparing non-equivalent taper schedules and doses not licensed conflates differences. This correction prevents misleading inferences about long-term flare-free probabilities.	Matters of opinion, not factual error.

Issue 4 Multiple modelling errors identified

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 8, 11, 14, 16, 21, 26, 27, 112, 113, 114, 118, 130, 134, 135, 138, 139, 140, 143, 147, 148, 149, 150, 177 – Throughout multiple sections of the EAG report, the text refers to ‘<i>multiple modelling errors</i>’ in the company’s cost-effectiveness analysis, implying that these points represent implementation mistakes rather than deliberate methodological choices.	The company suggests to replace the term ‘errors’ in Errors 01, 02, 04, 05, 06, and 07 with ‘<i>EAG preferred assumptions</i>’	The word “errors” misrepresents the issue and could inappropriately reduce confidence in the company submission. Whilst it is acknowledged and understood that the EAG have preferred assumptions for modelling, we make this suggestion to ensure the report is read with accuracy. Terminology such as ‘errors’ used imprecisely risks undermining the reader’s confidence in the model’s accuracy. In reality, each of the points reflect an assumption or alternative methodology supported by precedent in NICE appraisals or by advisory-board input; reframing them as assumptions clarifies these	No factual error. No revision needed. As per the EAG report the EAG still thinks these are errors.

		approaches are open to debate rather than modelling errors.	
Error/EAG preferred assumption 01:			
Page 26 – The EAG report title <i>‘Error 01: Not taking into account baseline cumulative steroid use.’</i>	The following changes are requested to the EAG preferred assumption 01. Amend the text on page 26 to: <i>‘EAG preferred assumption 1: Assuming relapsed patients in the ITT population have a baseline cumulative steroid dose.’</i>	To aid clarity when interpreting the EAG’s preferred assumptions.	No factual error. No revision needed. The entire model structure and assumptions of the company base case for the modelling of steroid related events are based upon applying the total cumulative steroid dose to date.
Table 14 – The EAG report uses the mean duration of diagnosis of the relapse population of SELECT-GCA to produce a weighted average cumulative dose for the ITT	The company suggests using the median duration of diagnosis in the proposed assumption in the EAG report to include an estimate of the cumulative steroid burden for relapsed patients	Using the median is a more methodologically appropriate and robust approach as it is not as sensitive to outliers as the mean is (i.e., reflects the middle of the distribution regardless of how long or short individual disease durations are).	The EAG will provide a scenario analysis that applies the median steroid duration of the SELECT-GCA relapsed population.

Page 114 – the EAG report misinterprets the longer-term impact of flares on mortality by applying Therkildsen et al. mortality multipliers as 1.03 in remission and 1.49 only during a 4-week flare.	Company suggests amending the text on page 114 to clarify that Therkildsen et al. report a relative risk of 1.49 over the first year following a flare, with a risk of 1.03 thereafter , rather than 1.49 applying only during a 4-week flare period.	The current text included in the report is not accurate.	The EAG accepts the proposed amendment
Error/EAG preferred assumption 02:			
Page 134 – The EAG report states: <i>‘only those on steroids in any given cycle are at risk of steroid-related adverse events,’</i> implying zero risk for all off-steroid patients without distinguishing those in sustained remission after tapering.	Company requests correcting the text in section 3.2.6.8 to read: <i>‘All patients carry risk of steroid-exacerbated conditions based on their cumulative steroid exposure, except those in pre-flare remission who have completed tapering or in post-flare remission off steroids.’</i>	To increase accuracy.	No factual error. No revision needed. The EAG thinks that its wording is clearer than that of the company. The company appears to suggest that there is a distinction between those in sustained remission who have completed tapering and those who have flared and completed tapering, yet its proposed wording does not make any distinction between these two groups.

Page 136 – The EAG report states: <i>‘But it does not seem reasonable to assume that only those receiving steroids can develop T2DM, or osteoporosis or the like. The EAG also thinks that it would be incoherent for the risk of a condition for those on steroids to be a function of their total cumulative steroid dose to date but for this risk to fall to zero once tapering has been completed despite their total cumulative steroid dose to date’.</i> This text is misleading as it does not account for the evidence in the literature supporting the company’s assumption.	AbbVie requests that the EAG reference these findings in the literature to maintain accuracy and facilitate effective decision making. Dixon et al. 2012,¹ supports the fact that discontinuing steroids greatly decrease the risk of corticosteroid related adverse events. The authors conducted a case-control analysis to explore the relationship of serious infection risk with current and prior oral glucocorticoid in elderly patients with rheumatoid arthritis (RA). The results show the impact of cumulative steroid burden by showcasing that a 5 mg steroid carries a 11%, 30%, or 55% increased risk of infection compared to the control arm if taken for 1,3, or 12 months, respectively, and that the same dose taken for 3 years would lead to 100% risk increase. The authors also explored the impact of glucocorticoid discontinuation and showed that 5 mg of steroids taken for 6 months is	Evidence in the literature and clinical validation confirms the risk of steroid related adverse events returning to the same level (or close to) as matched controls has clinical validity. Therefore, modelling patients who are not on steroids as having no risk of developing these adverse events is a sensitive simplification made to avoid introducing the complexities of modelling different incidences observed in the general population for 34 adverse events. Therefore, clarifying these two exemption groups (pre-flare and post-flare remission off steroids) makes the model’s at-risk population transparent and aligns with real-world evidence.	No factual error. No revision required. The company acknowledges that the absolute risk does not fall to zero upon cessation of steroids. The EAG will add additional text to section 5.2.7. Note that the odds ratio falling to 1.06 (Dixon) and the hazard ration falling to 1.00 (Movahedi) after cessation of steroids supports the EAG contention that the risks of steroid use after cessation of steroid use abate for at least some conditions. This calls into question the company base case modelling and model structure.

	associated with OR of 1.46 compared to non-steroid users, but that this risk falls to only 1.06 following 6 months after discontinuing steroids. Using a similar approach Movahedi et al. 2016,² used to distinct data sets (including UK CPRD) to assess risk of diabetes in RA patients receiving corticosteroids. Their findings show patients who received 5 mg per day for 6 months have an adjusted HR of 1.48 compared to non-users, and importantly, that this risk returns to baseline (HR 1.00) 3 months after stopping.		
Error/EAG preferred assumption 03:			
The EAG amended model inadvertently adds a mortality multiplier in the trace of each treatment arm (EW, EY, FC, FE and FG columns).	Company suggests correction of this error such that the extraneous mortality term should be removed so that mortality is applied only once per cycle when patients exit each health state.	AbbVie acknowledges and accepts the error pointed out in the EAG report. However, in completing the accuracy check it was noted that because cycle mortality is already applied when patients transition out of each health	No factual error. No revision required. The company has withdrawn this issue.

		state, the additional mortality factor double-counts deaths (albeit at a small absolute level due to small probability of long-term death) artificially inflating complication incidence over time. Removing the duplicate mortality application ensures the calculation properly reflects only the single intended mortality adjustment and yields plausible cumulative incidence values.	
Error/EAG preferred assumption 04:			
Page 134 – The EAG report observes that the company model converts annual incidences of glucocorticoid-related adverse events (e.g., dyspnoea) into weekly probabilities using the standard formula $p_{\text{weekly}} = 1 - (1 - p_{\text{annual}})^{7/365.25},$ but then does not reduce the eligible population by the	Company suggests replacing the sentence in the narrative with the following clarification: <i>‘This weekly conversion follows standard practice for state-transition models with short cycle lengths but represents a simplification, as it does not dynamically adjust the at-risk population within each cycle. While this may introduce a small upward bias at higher event rates, it is an accepted approximation when source</i>	Although the EAG’s original wording implies that a full ‘survival-style’ risk-set adjustment should have been implemented, in practice most HTA state-transition models apply the simple annual-to-weekly conversion without within-cycle population reduction (according to ISPOR-SMDM Good Research Practices and other modelling	No factual error. No revision required. The EAG does not suggest a full survival analysis should have been applied. It clearly states that the correct method is to simply divide the annual incidence by 52 to yield the weekly incidence.

weekly incidences of events and suggests the ' <i>total incidence of events over the year is overestimated</i> '. In this, the EAG report does not acknowledge this approach as a modelling simplification.	<i>data are reported as annual probabilities.'</i>	guidelines). ³⁻⁵ Acknowledging this approach as a modelling simplification makes the method transparent, accurately characterises the source of any small bias, and aligns the report with established health-economic practice.	
Error/EAG preferred assumption 05:			
Page 135 – The EAG report states that, in the model, once upadacitinib is stopped at two years, patients in the upadacitinib arm continue to follow the 26-week glucocorticoid taper originally applied during the treatment period, rather than switching to the longer 52-week taper used elsewhere for treatment discontinuation. This was characterised as inconsistent ' <i>modelling error</i> ,' implying the taper duration should have	The company suggests reframing the 'error' to reflect that this was an intentional company-selected assumption.	The company accepts that the EAG report has raised the different tapering schedules as a concern, and whilst AbbVie agrees that the same tapering schedule across both arms would be useful, capturing it as an 'error' may not fully reflect the intentionality behind this company-selected assumption.	No factual error. No revision required. The EAG still thinks that this is an error. It will add text to section 3.2.6.9 noting that the company disputes this.

extended to 52 weeks after drug cessation.			
Error 06/EAG preferred assumption 06:			
Page 135-137 – The EAG report states that the model <i>‘the daily steroid dose tails off as patients age. This is due to the daily dose not being conditioned by survival,’</i> implying that steroid doses may be inappropriately applied to patients after death and that risks of adverse events are misallocated. The EAG further comment on an issue related to Error/Assumption 02 and states that <i>‘it does not seem reasonable to assume that only those receiving steroids can develop T2DM or osteoporosis,’</i> and that <i>‘it would be incoherent for the risk of a condition for those on steroids to be a function</i>	Company suggests revising the text to read: <i>‘Steroid exposure in each cycle is calculated as the average dose per health state multiplied by the proportion of the cohort alive in that health state, ensuring that deceased patients do not contribute to mean dosing. The observed decline in mean dose over time reflects both transitions to ‘no-steroid’ health states and fewer survivors requiring steroids, not inadvertent averaging across deceased patients.’</i> Additionally, the company suggests stating that the EAG has a preferred approach on how to calculate the cumulative steroid dose. AbbVie request the EAG amends the comment related to Error/Assumption 02 to reflect the factual inaccuracy stated in the respective problem and proposed amendment.	This is a factual inaccuracy as the model correctly conditions steroid dose on survival. By explicitly describing survival-conditioning the report will more accurately convey the model’s mechanics and pre-empt misinterpretation of dose calculations.	The EAG does not think this an error but has asked for further clarification from the company. To be clarified.

of their total cumulative steroid dose.'			
On page 135 the EAG report states: <i>'The daily steroid dose tails off as patients age. This is due to the daily steroid dose not being conditioned by survival.'</i> This statement is misleading as the daily steroid dose is conditioned by mortality.	We propose the following amendment: <i>'This is due to the mean steroid dose not being conditioned by survival.'</i>	To aid clarity. Whilst the calculation of the mean steroid dose is not conditioned by survival, the daily steroid dose includes mortality calculations. These take place in the calculations as patients transition through health states. Therefore, the original statement is misleading.	No factual error. No revision needed. This is clearly explained in Table 31 which the company has not identified any issue with. The EAG will add additional text around this to underline the EAG correction to the calculation; i.e. the steroid dose that should be calculated is that relevant to the surviving patients and not to the cohort as a whole when assessing the risks of steroids among the surviving patients.

Issue 5 For the new onset subgroup should treatment sequencing be modelled?

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 139, 157 – The EAG report highlights that for the new-onset subgroup the company’s model compares only upadacitinib plus a 26-week steroid taper versus placebo plus a 52-week taper, without allowing patients in the placebo arm to switch to tocilizumab or upadacitinib upon relapse. The EAG preliminarily speculates that ‘these expensive therapies’ should be reserved for relapsing patients (thus implying modelling treatment sequencing) and speculates this could be more cost-effective.	The company suggest that the EAG report reflects that incorporating the treatment sequencing would add unnecessary complexity and increase uncertainty. Additionally, the wording in the report should capture that the impact of relapse is implicitly captured in the modelling of the relapsed population.	To aid understanding on why treatment sequencing was not pursued in the base case by the company, AbbVie consider the amendments to be critical. Sequencing analyses without robust IPD and comparative effectiveness estimates would depend on highly uncertain assumptions (e.g. independence of flare hazards and constant relative treatment effects in later lines), risk producing misleading ICERs, and impose substantial additional modelling complexity. Also, it should be noted that relapsing cohort already captures the post-flare experience for patients who progress on steroids alone.	No factual error. No revision needed. It may add complexity but it is not clear that this would be unnecessary complexity. The EAG will add text to section 5.1 (Section 5.2 in post FAC report) to reflect the concerns of the company.

Issue 6 How should the time to first flare for the new onset subgroup be modelled?

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 23 – The EAG report mentions the company base case assume upadacitinib is assumed to be disease modifying and further expert opinion is required on whether this is the case or if there would be a waning of the treatment effect. This statement could be considered misleading as the company did not assume upadacitinib is disease modifying with a permanent reduction in flares.	The company suggests amending the following text <i>‘The company base case selects the Gompertz curves without waning the treatment effect after cessation of upadacitinib use. These plateau from year three causing the model to estimate that 20% more patients in the upadacitinib arm will avoid flaring in perpetuity. The company advisory board suggests that if upadacitinib use is continued indefinitely then the plateauing of the Gompertz may be reasonable.</i> <i>EAG expert opinion is that upadacitinib is unlikely to be disease modifying so when stopped at 2 years the upadacitinib curve will converge towards the placebo curve.’</i> To <i>‘The company base case selects the Gompertz curves and applies a piecewise approach to account for immediate loss of efficacy of upadacitinib once the treatment is</i>	Correction of a factual inaccuracy. The Company Submission explicitly describes the instantaneous hazard switch after patients discontinue treatment, at two years in the base case (CS p. 55). It will also aid clarity for the reader if it is clear the EAG’s concern is around how treatment waning is modelled than the company suggesting upadacitinib is disease modifying	No factual error. No revision required.

	discontinued. As the placebo curve plateau from year three, the model estimates that 20% more patients in the upadacitinib arm will remain flare free. The company advisory board suggests that if upadacitinib use is continued indefinitely then the plateauing of the Gompertz may be reasonable. EAG expert opinion is that after upadacitinib is stopped at 2 years the upadacitinib curve will converge towards the placebo curve.'		
Section 5.2.3, page 161 – The EAG report incorrectly suggests the company model assumes unwaned, disease-modifying effect for upadacitinib.	Company suggests revising the text to explain that the base-case does <u>not</u> assume upadacitinib is disease modifying and as such employs a piecewise approach to account for the immediate loss of efficacy of upadacitinib once the treatment is discontinued. The company suggests the report clarifies how the piecewise approach work: 'The upadacitinib Gompertz curve is applied to the TTFF for the first two years of treatment, and upon discontinuation, the model instantly switches the probability of first flare to	Correction of a factual inaccuracy. The Company Submission explicitly describes the instantaneous hazard switch after patients discontinue treatment, at two years in the base case (CS p. 55), and clinical experts endorsed the Gompertz shape for the placebo arm. It should be noted that this curve selection and extrapolations align with findings from the advisory-board in which clinicians confirmed that predicted five-	No factual error. No revision necessary.

	<i>match the placebo arm, to match the same hazard fitted to the placebo arm. Both curves follow a Gompertz distribution and plateau by year three, reflecting that later flares become increasingly rare. The constant vertical offset preserves the early benefit rather than implying eternal waning-free protection.'</i>	year flare-free proportions of approximately 25-32 % in the placebo arm align with real-world expectations. It is important to clarify that the company does not claim upadacitinib is disease-modifying in the base case (and that indefinite treatment scenarios were explored only in sensitivity analyses) and ensures that the report accurately reflects the model structure, the trial data as well as the advisory board's consensus.	
Page 162 – The EAG report states: <i>'Waning of effect can be explored by forcing convergence of the TTFF curves over a specified timeframe; e.g. 8 years waning from year 3 as shown in Figure 65', thus implying upadacitinib</i>	AbbVie requests the text to be revised or amended to the following sentiment: <i>'Waning of effect can be explored by forcing convergence of the TTFF curves over a specified timeframe, e.g. 8 years waning from year 3 as shown in Figure 65. However, this forcing the convergence of the curves would imply upadacitinib patients experiencing a higher first-flare</i>	To clearly articulate that upadacitinib prevents flares during treatment but there is no evidence to suggest that treatment with upadacitinib will induce an increased rebound susceptibility upon cessation. This assumption has no clinical plausibility and the wording in the report	No factual error. No revision required. The EAG will add a summary of the two papers that explore cessation of tocilizumab treatment to section 5.2.3.

patients experience a higher first-flare hazard than placebo after discontinuation.	<i>hazard than placebo after discontinuation, which is clinically implausible as there is no biological or clinical rationale for assuming a rebound hazard above the CS-only rate once treatment stops.'</i>	should be amended to reflect this.	
Page 70 – The EAG report compares 3-year KM estimates from GiACTA to the SELECT-GCA extrapolations without acknowledging differences in trial design. The EAG report does not clearly state which arms of the GiACTA trial are mentioned as in some instances the EAG report presents pooled data of the placebo arms and tocilizumab.	Company suggests inserting a paragraph immediately after the GiACTA comparison to note: <i>'These cross-trial comparisons should be interpreted cautiously due to differences in trial design including a broader flare definition (symptom recurrence ± biomarker rise) that did not require corticosteroid dose escalation. SELECT-GCA's flare definition is more stringent: symptoms (or ESR >30 mm/hr) must also prompt a CS dose increase. Therefore, the two KM curves are not directly comparable.'</i> AbbVie requests the EAG report to specify which arms of the GiACTA trial are presented; without this information the company is unable to comment on	To increase accuracy, the company requests the incorporation of the additional text which makes explicit why the ~42 % GiACTA KM and ~52 % SELECT-GCA/log-normal estimates cannot be taken as a like-for-like validation. Acknowledging the different trial design, particularly flare criteria, prevent over-interpretation of the GiACTA data and aligns with best practice in cross-trial contextualisation.	No factual error. Since the company's submission includes only 1 year observed data, cross trial comparisons with potentially longer follow up provide information of likely interest to the appraisal committee.

	the factual accuracy but highlights above the issues with this approach.		
Page 71 – The EAG report states: <i>‘the short follow up and few participants in the new-onset subgroup represent limitations that make it difficult to decide which, or if any, of the available models can be used with confidence in determining long term outcome for TTFF’</i> which understates the rationale for selecting the Gompertz model and omits validation and cross-trial context.	Company suggests replacing ‘few participants’ or augmenting the existing sentence to that effect, with: <i>‘While the short follow-up and small size of the SELECT-GCA new-onset subgroup (although higher number of new-onset patients than in GiACTA) limit precision, the company’s modelling decision was informed by both statistical fit and clinical consensus. Of the two candidate curves (Gompertz vs log-normal), five independent GCA experts preferred the voted in favour of Gompertz curve for its ability to capture early flare dynamics. The company also validated projected lifetime flare counts against real-world cohort data, finding close alignment.’</i>	To clarify that the following points: a) Clinical experts (n=5) endorsed Gompertz b) Lifetime flare projections were externally validated, and c) SELECT-GCA new onset subgroups had a larger sample size than GiACTA, Thereby strengthening the justification for the chosen model.	No factual error. The ERG has replaced ‘few participants’ with ‘small number of participants’.

Issue 7 Is the modelling of GCA flare related complications accurate?

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report state issue 7 as ‘Is the modelling of GCA flare related complications accurate?’ This title could lead to misinterpretation of the issue	Amend the title of the issue from: <i>‘Is the modelling of GCA flare related complications accurate’</i> To read: <i>‘Is the source of GCA flare related complications valid’</i>	To aid clarity that the concern relies within the <i>source of the data</i> rather than the <i>modelling</i> approach.	No factual error. No revision required.
Section 5.2.5 – The EAG report notes that the rates used for GCA flare-related complications derive primarily from incidence at initial diagnosis or from broad associations with GCA, and that expert opinion suggests true complication rates are lower at subsequent flares once patients are managed and educated. However, the report does not acknowledge that the	AbbVie request the EAG report amends this text: <i>‘EAG expert opinion is that rates of complications at presentation are somewhat higher than at subsequent flares due to diagnosing of preexisting conditions, the conditions being the reason for presentation and patients being better controlled and better educated by the time of any subsequent flares.’</i> To read: <i>‘Although the company follows the same approach that was deemed as</i>	To aid clarity that this approach was deemed appropriate in TA518	No factual error. No revision required. The importance of and modelling of GCA flare related complications within TA518 to Committee is unknown. It is correct that the TA518 FAD did not identify this as an issue. This does not mean it is not an issue for the current assessment

Company approach was aligned with the accepted approach in TA518.	<i>appropriate in TA518 by incorporating annual incidences based on incidence at initial diagnosis, EAG expert opinion is that rates of complications at presentation are somewhat higher than at subsequent flares due to diagnosing preexisting conditions, the conditions being the reason for presentation and patients being better controlled and better educated by the time of any subsequent flares.'</i>		

Issue 8 Does the effect of steroids on risk of complications abate when off steroids?

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.2.6 – Issue 8 in the EAG report is labelled as ‘ <i>Does the effect of steroids on risk of complications abate when off steroids</i> ’ – the title is misleading as the highlighted issue is different.	The company suggests amending the title of the issue to ‘ <i>Should the risk of all steroid related complications be a function of the total cumulative steroid use to date</i> ’	To aid clarity. The current title implies the issue is regarding what happens to the effect when patients are off steroids. However, the proposed approach and analyses performed in the EAG report suggests the uncertainty is about what drives the risk of these AEs (i.e. whether it's the total cumulative steroid	No factual error. No revision required. As previously noted the EAG will add text highlighting the results of Dixon and Movahedi on the effects of cessation of steroid.

		use to date or a function of the average steroid dose in the preceding year.)	
Section 5.2.6 – The EAG report states that expert opinion suggests that ‘associating an increased risk with total cumulative steroid dose since baseline’ is less reasonable for transient conditions rather than permanent conditions. This statement is not consistent with published literature.	The company requests amending the text to: <i>‘EAG expert opinion also suggests that associating an increased risk with the total cumulative steroid dose since baseline may be reasonable for conditions where the damage is permanent, such as osteoporosis. But it is less reasonable for conditions where the risks of developing these adverse events abate after steroid use is stopped, EAG expert opinion suggests the following conditions (...). Nevertheless, the literature has consistently shown a link between the cumulative steroid burden with many transient steroid-related adverse events.</i> <i>To explore the impact of these assumptions, the EAG explores revising the risks of these to be dependent upon the total steroid dose of the previous year rather than the total steroid dose since diagnosis.’</i>	To aid clarity, the report should acknowledge that the literature has shown an increased risk in steroid related adverse event linked to the cumulative steroid dose in transient adverse events. As an example, Mar Pujades-Rodriguez et al⁶ show the five-year cumulative risk increase of cardiovascular diseases from 7.1% to 28% in patients with immune mediated inflammatory diseases and Dixon et al., show the risk of serious infections in older patients with RA taking 5mg daily of prednisone has a 30%, 46% and 100% increase if taken continuously for 3 months, 6 months or 3 years respectively.	No factual error. No revision required. As previously noted the EAG will add text highlighting the results of Dixon and Movahedi on the effects of cessation of steroid.

	The company also requests including the sources mentioned in the justification as references to the added text.		

Issue 9 Does the modelling of steroid related conditions have face validity?

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report describes Key Issue 9 as ‘Does the <i>modelling</i> of the steroid-related conditions have face validity?’ can be perceived as potentially misleading and conflates concerns with the <i>model</i> as opposed to the <i>data source</i> .	Company suggests amending the title of issue 9 from: ‘Does the <i>modelling</i> of the steroid-related conditions have face validity?’ To read: ‘Does the source used to model the steroid-related conditions have face validity?’	To aid clarity that the concern relies within the <i>source of the data</i> rather than the <i>modelling</i> approach.	No factual error. No revision required.
The EAG report describes in Key Issue 9 that the annual incidence of the RWE should be aligned to the SELECT-GCA trial; however, the incidence does not match.	Company suggests amending the following text: <i>‘The model annual incidences are derived from an analysis of a US Health Insurance database data on GCA patients in the year after their</i>	It is misleading to imply that annualised incidence of steroid-related AEs could be reasonably determined through a one-year RCT and this should be contextualised in the EAG report.	No factual error. No revision required.

This could be misleading as literature supports the fact that RCTs have shown little or no increased risk of steroid related adverse events, contrary to RWE and established expert opinion.	<i>diagnosis so should be aligned with SELECT-GCA data for the new onset subgroup. The modelled annual incidences are typically large multiples of the SELECT-GCA ITT population incidences'</i> To read: <i>'The annual rates of steroid-related conditions in the model derive from a large US study of newly diagnosed GCA patients, following TA518 committee's preferred source to inform these incidences. The company stated in their submission how, similar to GiACTA, in SELECT-GCA the rates of these adverse events were low due to the nature of controlled trials. The company also highlights these incidences were validated by clinical experts during the advisory board and, where available, against UK clinical literature Nevertheless, the modelled annual incidences are typically large multiples of the SELECT-GCA ITT population incidences.'</i>	For reasons previously stated in the CS, RWE was deemed the best source to inform this following TA518 committee's preferred source. These real-world incidence estimates were reviewed and confirmed by healthcare professionals through an advisory board and are supported by UK epidemiological studies reporting similar rates. Lastly, the literature shows RCTs don't fully capture the burden of these adverse events due to the controlled nature of clinical trials.	

Page 46 – The EAG report states <i>‘this RWE study [Curtis et al. 2025] was not listed among the included observational studies presented in CS Appendix B, Table 25. There was therefore a disconnection between the company’s SLRs and the evidence that was used to inform the company’s economic modelling.’</i> Page 47 states <i>‘Notably, this additional search conducted by EAG, did not retrieve [this] RWE study’</i>	Company suggests revising the sentence to read: <i>‘Curtis et al. (2025) was published after the company’s systematic-review cut-off date and therefore could not have been captured in Appendix B, Table 25’.</i>	It is factually incorrect to imply that the study was omitted despite being available as Curtis et al. (2025) became available only in July 2025,⁷, thus after the company’s submission. The timing of its publication explains its absence from Appendix B. By noting its publication date and the company’s proactive sharing of the unpublished manuscript, this amendment corrects the factual record, demonstrates that the model inputs were indeed drawn from that RWE source, and removes any implication of an unwarranted evidence gap.	No factual error. The quoted EAG statement was to highlight the disconnection between the company’s SLRs of <i>published</i> literature and its economic modelling.
In page 52 – The EAG report highlights that no significant differences in corticosteroid related AEs were observed between the trial arms with a wording that could be perceived as	The Company request amending the text: <i>‘Importantly, no significant difference in corticosteroid related AEs were observed between the trial arms, even for those with relatively common</i>	To aid clarity that the results shown in SELECT-GCA match what has been observed in previous RCTs.	No factual error. No revision required.

suggestive there would be no difference in longer term steroid related AE burden.	occurrence.' To read: <i>'As observed in other RCTs and acknowledging the controlled conditions of these studies, no significant differences in corticosteroid related AEs were observed between the trial arms in SELECT-GCA, even for those with relatively common occurrence'</i>		
Page 13 – The EAG report states: <i>'no significant differences in the steroid related adverse events between the trial arms were observed and that while an association between cumulative exposure to steroids and its associated adverse events has been observed, the extent to which Upadacitinib may reduce these adverse events remains to be demonstrated'</i>	The company requests to amend the following text: <i>'In addition, despite that upadacitinib significantly reduced cumulative steroid use compared to placebo during year 1 of the trial, no significant differences in steroid-related adverse events were observed. While the association between cumulative exposure to steroid and its associated adverse events has been well reported in observational studies, the extent to which upadacitinib (and other steroid-sparing treatments) may reduce steroid associated adverse events remain to</i>	Same as above.	No factual error. EAG's statement merely highlighted the importance of demonstrating hypothecated benefits with empirical evidence.

The wording is suggestive and undermines upadacitinib mechanism of action and results.	<i>be demonstrated by trial evidence given the clear potential of confounding by disease severity.</i> To read: <i>'In addition, despite that upadacitinib significantly reduced cumulative steroid use compared to placebo during year 1 of the trial, no significant differences in steroid-related adverse events were observed. This effect has been previously seen in other RCTs, including GiACTA, where tocilizumab had a higher proportion of patients with these adverse events. Nevertheless, the association between cumulative exposure to steroid and its associated adverse events has been well reported in observational studies'</i>		

Issue 10 How often do patients visit rheumatology when tapering their steroids?

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.4.1 – The EAG report questions the ‘<i>face validity</i>’ of the company’s rheumatology visit estimates during steroid tapering, noting that they rely on a ‘<i>largely undocumented</i>’ market survey cited in TA518.	The company suggests removing any reference to ‘<i>undocumented</i>’ market survey.	To emphasise that TA518 is a publicly referenced NICE appraisal whose EAG and Committee deemed its market survey-based visit frequencies appropriate for policy decisions and therefore should not be represented as an ‘<i>undocumented</i>’ analysis. Characterising these estimates as methodologically opaque undervalues the Committee’s prior validation. By reaffirming TA518 as the principal, authoritative source and labelling alternative frequencies as exploratory, the report will accurately attribute data provenance and preserve consistency with established NICE practice.	No factual error. No revision needed. Section 5.4.1 does not question “the face validity” of the company’s rheumatology visit estimates. The TA518 survey is largely undocumented. The EAG could find little to no detail of it other than the final resource use tables in TA518. It is fair to describe it as “minimally documented”.

Issue 11 Model Results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 18 (ITT population group): Placebo total costs are reported as [REDACTED] but should be [REDACTED]	Update the placebo cost in the ITT population group on page 18 from [REDACTED] to [REDACTED]	Corrects a numerical error and restores consistency with the model's base-case cost inputs (see Company base case costs, Table 2)	The EAG accepts the proposed amendment.
Page 153, Table 48 ('Scenarios around EAG corrected company base case'): the 'No severe flares' row currently reports ΔCosts [REDACTED]; ΔQALYs [REDACTED]; ICER £24,490	In Table 48 on page 153, amend the 'No severe flares' row to read ΔCosts [REDACTED]; ΔQALYs [REDACTED]; ICER £24,353	Corrects a numerical error and ensures consistency with the underlying EAG corrected scenario-analysis outputs for 'No severe flares'	The EAG accepts the proposed amendment.
Pages 185-186, Table 68 (SA07c): the ITT ICER for 'SA07c: 20% secondary flare annual incidence' is reported as £48,818 but should be £48,812	In Table 68 on pages 185-186, amend the SA07c ITT ICER from £48,818 to £48,812	Corrects a numerical error in the EAG's scenario-analysis outputs for SA07c	The EAG accepts the proposed amendment.
Pages 185-186, Table 68 (SA02): the Company cannot reproduce the SA02 results ('Subset	Revise Section 5.2.6 to explicitly list and define all conditions included in SA02, and update Table 68 if any additional elements materially alter the	Ensures transparency and reproducibility of the SA02 scenario by matching the	No factual error. No revision required. The last paragraph of section 5.2.6 specifies

complications prev. year steroids') because the subset of conditions is not fully specified in Section 5.2.6	SA02 results (currently £99,103 ITT, £76,142 new onset, £211,139 relapsed)	analysis to the fully specified model inputs	the list of conditions, though the EAG acknowledges that it may not have been clear the "infections" include both opportunistic infections and infections requiring hospitalisation. The conditions are defined in the EAG revised economic model by using the dropdown in EAG worksheet cell B6. This causes the SA02 EAG assumptions to be changed, for SA02 in cells E64:E96. The user then needs to revise the values in B64:B96 so that the values in F64:F96 all read TRUE.
Pages 185-186, Table 68 (SA06a–d, SA06f): the relapsed-group results for SA06a, SA06b, SA06c, SA06d and SA06f are reported as £125,759, £127,423, £126,834,	In Table 68 on pages 185-186, amend the relapsed-group results for each of SA06a, SA06b, SA06c, SA06d and SA06f to £130,303	Corrects multiple numerical errors to ensure all SA06 scenario costs reflect the correct outputs for the relapsed subgroup.	The EAG accepts the proposed amendments.

£126,382 and £126,174 respectively but should each be £130,303			

Issue 12 Recreated TTFF Plots

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 2.5 Pages 57, 67 and 73- The EAG report states that the difference in the start numbers at risk between the EAG's TTFF plots and the company's may be due to patients being coded at zero days and were lost from the analysis. This is factually inaccurate.'	The company requests to amend the following text '<i>A difference in the EAG plot from the company clarification figure is the start numbers at risk; this may be due to some patients being coded at zero days and were lost from the analysis</i>' To <i>'The difference in the EAG plot from the company clarification figure is the start numbers at risk; this is due to the Company following the approach used in TA518, a recognized approach in censoring literature, where patients were censored at day 1 and not at baseline'</i>	It is factually inaccurate. As detailed in the CQs, the company followed the approach followed in the Tocilizumab submission to NICE, TA 518 where patients were censored at day 1 and not at baseline. This censoring is in line with recognised censoring methods. ⁸	Not a factual error. The EAG carefully used the words "may be due to". The reason this wording was necessary being the very late supply of correct KM data by the company together with a lack of clarity in the company's late data supply.

Issue 13 Indirect treatment comparison

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, 2.3, 2.5 and throughout the report when discussing a comparison to tocilizumab – the EAG report includes statements akin to: <i>‘The company submitted no information about tocilizumab’ – are factually inaccurate.</i>	The company proposes to include the justification as presented in the submission and during CQs on why a comparison to tocilizumab was not presented. We suggest also capturing the following key points: 1) Upadacitinib is being appraised for adult patients with GCA over their lifetime; the company are not presenting a fixed ‘stopping rule’, but instead positioning upadacitinib as a flexible treatment option with duration defined by patient disease activity and clinician judgement - given GCA is a recurrent, chronic condition, this limits the relevance of tocilizumab: Tocilizumab is restricted for patients with GCA relapse and has a fixed one-year stopping rule; the published evidence suggests that patients frequently experience high relapse rates following treatment	Factual inaccuracy. The current text in the EAG report does not include the justification on why a comparison versus tocilizumab was not included and thus can be misleading. It is important to include the full rationale from both the company and EAG perspective so that the reader may more thoroughly assess the relevance of tocilizumab to the decision problem	No factual error. No revision required.

	cessation. Furthermore, tocilizumab is not recommended for patients who have previously received the treatment, meaning patients must return to corticosteroid therapy in England. As a result, tocilizumab is a short-term treatment for only a limited number of patients, and is considered to be of relevance for only a fraction of the population and time horizon being considered in this current appraisal. 2) Whilst the administrative challenges related to limited use of tocilizumab in clinical practice are noted by the EAG, it is also important to note that this judgement is supported by multiple sources, including clinical expert consultation (advisory board), NICE scope consultation responses and the Getting It Right First Time (GIRFT) NHS programme.		
Section 2.5.1.1 TTE data – The EAG report states that	The company requests provision of further details on why a 40-fold	Textual clarification	ERG have changed text to “...extensive

<i>'The base case life-time economic model required a 40-fold extrapolation beyond observed data'.</i> The company base case analysis models a lifetime horizon reflecting 28 years duration; it is not clear to the company why the EAG produced the 40-fold extrapolation figure based on 52-week observation period of SELECT-GCA.	extrapolation is required or amend to reflect the number of years in the model's life-time duration		extrapolation beyond one year trial data".
Section 2.5.1.1 TTE data: the EAG report provides criticism of limited patient numbers and trial follow up period calling the evidence based 'relatively weak'	Company requests amending the following statement: <i>'As such the EAG considers the data base relatively weak'</i> To: <i>'Acknowledging the limitations of clinical trials, the EAG considers the company relied heavily on clinical advice to establish valid modelling due to small population sample size and limited follow-up. Nevertheless, the EAG recognises GiACTA had fewer patients in their trial and was subject to same of uncertainties'</i>	To aid clarity. AbbVie accepts the EAG's criticisms, however, the company do not consider frequent limitations of clinical trials informing NICE appraisal. The report includes multiple comparisons between SELECT-GCA and the GiACTA trial and as such should acknowledge both trials are subject to similar challenges.	No factual error. Regarding GiACTA, in analyses presented by the ERG all "at risk tables" were included in graphs to ensure that readers take patient numbers into account when interpreting the findings. .

Section 2.5.1.2 – The EAG report mentions the following <i>‘This suggests presence of two or more subgroups with distinctly different TTFF properties and renders it unlikely that parametric models with limited flexibility will provide good fit to the PBO data’</i>	Company suggests removing the supposition that it’s <i>‘unlikely that simple parametric models will provide a good fit to the data’</i>.	To aid clarity. AbbVie acknowledge that it’s certainly possible that more flexible models provide a better fit to the data over the long term; however, models like log-normal and log-logistic can accommodate non-monotonic hazard functions and should not be discounted. More importantly, the company preferred extrapolations are selected based on clinical validation at the advisory board, from clinicians who were able to comment on the long-term flare rates and trends for UK GCA patients receiving steroids based on their real-world observations – clinical experts felt that the selected extrapolations provided an appropriate reflection of longer-term trends and should not be discounted	No factual error. This point is mainly about the wording of opinions.

Section 2.5.1.2 – The EAG report states ‘these results mean that the company’s strategy for TTFF depends almost exclusively on clinic advice’	The company requests that the external validation reported in the company submission against the literature also be noted in the EAG report.	Factual inaccuracy. As described in the company submission, the model predicted total flares at 5-10 years were also validated against literature reported values, as identified as realistic rates by the EAG in TA518	ERG doubt a factual error. The ERG statement is not quoted in full. The full quote is: these results mean that the company’s strategy for TTFF depends almost exclusively on clinical advice. In EAG opinion the resulting selection could be tested using available external evidence. The company’s “Validation” from TA 518 seems odd when the company excluded tocilizumab as a comparator.
Section 2.5.1.3 and throughout where comparison between the proportions of patients experiencing first flare	Where the EAG report compares the proportions of patients experiencing first flare based on trial extrapolations the company would request that the EAG report notes the inherent limitations with	The EAG report does not highlight the differences between the trial design and population and therefore does not acknowledge the	No factual error

between the SELECT-GCA and GiACTA trials are made.	the comparisons when presenting these throughout the report for reader transparency. These include - Fundamental differences in trial design: e.g. for SELECT-GCA flare was defined as an event determined by the investigator to represent recurrence of GCA signs or symptoms or an ESR measurement > 30 mm/hr (attributable to GCA) AND requiring an increase in CS dose; for GiACTA a flare event was defined as a recurrence of symptoms attributable to active GCA, with or without elevation of ESR and/or CRP. Therefore, SELECT-GCA places an additional requirement for an increase in corticosteroid dose to assign a flare, and may result in a key discrepancy in outcome assignment between trials. - Heterogeneity in patient populations	uncertainty of the comparison. Adding these clarifications ensures the reader has full context of the limitations and uncertainty of the presented comparison.	
Section 2.5.1.5: to The EAG performed a naïve comparison to compare	The company requests that the EAG reconsiders their framing and/or inclusion of the comparison between	It is methodologically inappropriate to compare SELECT-GCA with GiACTA	The ERG comparison is between four treatments:

SELECT-GCA with GiACTA Furthermore, the EAG compared the pooled PBO arm data from Stone et al. with SELECT-GCA PBO arm data alone. Whilst SELECT-GCA PBO arm included 52-week corticosteroid tapering alone, GiACTA pooled data included both 52- and 26-week corticosteroid taper regimens;	SELECT-GCA and GiACTA within the report. Furthermore, if the EAG wishes to retain a naïve comparison, it should be made clear throughout this section the following points: a) The fundamental differences between the study populations b) The GiACTA PBO arm data presented are using pooled data from GiACTA (52- and 26-week corticosteroid tapering arms) and acknowledge that it is clinically established that patients receiving the 26-week tapering regimen alone perform measurably worse and that this is not a treatment regimen reflective of UK clinical practice. As a result, the comparative outcomes may be biased.	using a naïve comparison due to fundamental differences between the study populations. These imbalances could bias comparative estimates and would therefore require population adjustment to obtain a fair comparison. It is also methodologically inappropriate to compare the pooled placebo arm of GiACTA with the placebo arm of SELECT-GCA as the results will be biased.	Upadacitinib, vs. PBO from SELECT-GCA and tocilizumab vs. PBO from GiACTA. A naïve comparison would only encompass upadacitinib vs tocilizumab. The report text has been changed so that “naïve” no longer appears. This involves text changes on pages 82, 84 and 87. We have included these comparisons because the ERG remains of the opinion that they are relevant for this appraisal and of potential interest to the appraisal committee.
Section 2.5.2: The EAG report states: ‘Participant characteristics were broadly similar	We request that the statement be amended to: ‘Participant characteristics were <i>not</i>	The statement is inaccurate. Based on the characteristics presented by the EAG in Table 14, and others not presented, it should be noted	Text changed to: Despite inevitable differences in the trial populations the EAG considers them to be

between the two trials' and that a higher proportion of patients were in remission at baseline compared to participants in GiACTA <i>'higher proportion in remission at baseline compared to participants in the GiACTA trial' is amended to reflect the differences in the trial design in regard to the criteria for remission.</i>	broadly similar between the two trials <i>as there were differences noted in characteristics such as age, and sex</i>'. <i>'A higher proportion in remission at baseline compared with participants in the GiACTA trial. Nevertheless, it is important to acknowledge that the criteria for remission were less strict in SELECT-GCA'</i>	that there are in fact substantial differences in key characteristics noted by clinicians to be treatment effect modifiers. The text citing the proportion of patients at remission risks being misinterpreted if no clarification of the different definitions is made.	broadly similar, and the analyses presented to be relevant for this appraisal. The following text was also added: "The company indicated in the FAC that the criteria for remission were less strict in SELECT-GCA."
Section 2.5.2: The EAG report describes an adjusted indirect comparison without details of how adjustment is applied, or which characteristics are considered.	AbbVie requests the required details to understand and appraise the adjusted ITC are reported, following reporting guidelines as described in the technical support documents of NICE Decision Support Unit or alternatively to refrain from presenting these results. If the report is amended to include the required reporting details of the ITC and the results are presented, AbbVie requests that following: • Detail any anchoring to the PBO arm in the comparison and	There are insufficient details to understand and critically appraise the EAG's analyses.	The EAG has now added the following text "using the standard method suggested by Bucher et al, with treatment effects anchored through the placebo arm of each trial." And have provided the reference for the methodology used for the adjusted

	include the potential impact of key differences between the SELECT-GCA and GiACTA PBO arms (e.g. substantial differences in cumulative corticosteroid dose as noted in Table 16). • In the conclusions of the section, acknowledge the high uncertainty of the results		indirect comparison in Section 2.5.2: Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997 Jun;50(6):683-91. doi: 10.1016/s0895-4356(97)00049-8. The data used in the EAG's adjusted indirect comparison were clearly presented in EAG report Table 15, Figure 29 and Figure 30.
Section 2.5.2.2.2: EAG report mentions: ' <i>In extrapolation lognormal and Gompertz models for the visually poor fit for PBO are almost identical while in</i>	AbbVie requests to amend figure 33 and 34 to show a lifetime extrapolation and to change the text to ' <i>Both Lognormal and Gompertz models are justifiable, in the extrapolation for PBO the models are almost identical while in contrast</i>	The EAG report makes statements about lifelong effect on flares; however, it is not possible to assess with the current level of data;	ERG do not think the company have identified a factual error.

<i>contrast there is a substantial difference between models for the upadacitinib arm where the Gompertz model implies that nearly 60% of patients will not experience FF during their lifetime while the PBO Gompertz model predicts continuing occurrence of FF during lifetime.'</i>	<i>there is a substantial difference between models for the upadacitinib arm where the Gompertz model implies that, at year 3, nearly 60% of patients remain flare-free and will not experience FF during their lifetime. The PBO Gompertz model predicts 'X' proportion of patients remain flare-free at year 3'</i> AbbVie requests the following statement in the EAG report includes the proportion of patients that remain flare free following the PBO Gompertz model in the text above and that the following statement is reviewed and corrected if needed 'and will continue to flare during their lifetime.'	further data is needed to avoid misinterpretation.	
Section 2.5.2.2.2: EAG reports presents GiACTA three-year data efficacy of tocilizumab versus placebo and performs an indirect treatment comparison.	AbbVie requests this section is not included in the report. If the EAG wishes to present the section AbbVie requests the following: The EAG report acknowledges the comparison is highly uncertain and is likely to artificially benefit tocilizumab due to the comparison against a pooled placebo arm (including the	It is inappropriate to provide crude comparisons including pooled placebo data from GiACTA (i.e., 52 weeks and 26-weeks). As the placebo response is worse in the 26-weeks, it is not appropriate to provide a comparison as the results will show an artificial benefit for tocilizumab.	Difference in opinions rather than factual inaccuracy. As previously stated, the EAG considers the analyses to be relevant for this appraisal.

	more aggressive 26-week tapering). Therefore, the findings are not suitable for decision making. • Provide the required details on the methodology used to conduct and indirect treatment comparison	Furthermore, there are no details on what type of indirect comparison was performed and no details on methodology to be able to appraise the appropriateness and robustness of the analysis and presented results	

Issue 14 Conditions exacerbated by steroid use (EAG issue 9)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In section 5.2.7, the EAG report state: <i>‘the major discrepancies of Table 55 render the company modelling of conditions exacerbated by steroid use largely meaningless,’</i>	AbbVie request to amend the wording in section 5.2.7 to: <i>‘While differences between the SELECT-GCA placebo arm and market-survey estimates of glucocorticoid-related adverse events reflect variations in patient characteristics, dosing patterns and reporting methods, the market survey remains a clinically credible source for real-world incidence. Table 55 illustrates these distinctions, which were explored and validated with clinical experts and aligned to literature where</i>	It is factually inaccurate to describe the RWE as meaningless. Whilst we fully acknowledge there are limitations with the generalisability of the RWE evidence to the current decision problem, the company have validated the RWE data with clinicians and UK literature where possible and followed the approach taken in TA518, where the committee recognised RWE as the most relevant source of evidence to inform corticosteroid-related AE	The EAG will revise the text to read: <i>Given the major discrepancies of Table 55 the EAG questions whether any weight can be placed upon the company modelling of conditions exacerbated by steroid use.</i>

Table 55 does not include the comparison with the literature provided by the company in A8.	available but does not invalidate the overall modelling of steroid-exacerbated conditions.' Furthermore, AbbVie request for table 55 to include the comparison with the available literature provided by the company in CQ A8.	burden. Discrepancies between trial and real-world data are expected as it is widely recognised in the literature that randomised controlled trials do not fully capture all corticosteroid-related adverse events. Acknowledging the differences between these data-source clarifies why Table 55 shows divergence without implying the model is 'meaningless.'	
In section 5.2.7: EAG report incorrectly states: <i>The controlled nature of clinical trials and frequency of patient follow-up might be expected to identify more rather than fewer incidences of conditions exacerbated by steroid use</i>	AbbVie requests this text to be amended to the following: <i>'the controlled nature of clinical trials and frequency of patient follow-up might be expected to identify more rather than fewer incidences of conditions exacerbated by steroid use. However, it also acknowledges that literature shows that RCTs consistently show fewer adverse events than observational studies.⁹ This could be explained by the fact</i>	The text is misleading as the literature shows observational studies have consistently shown increased risk for corticosteroid related adverse events.	The EAG will add text to section 5.2.7 to the effect that: The company thinks the real-world evidence may differ from that of the trial due to the trial following a rigorously defined steroid tapering schedule and escape criteria and a more stringent

	<i>that patients in trials follow a rigorously defined steroid tapering schedule and escape criteria and a more stringent inclusion/exclusion criterion.'</i>		inclusion/exclusion criterion. But given the major discrepancies this may beg more questions than it answers, particularly with regards the modelling of the incidence of flares which is what the model revolves around.
Section 5.2.7 – Company response to EAG question: <i>'The company was asked that baseline prevalences and new diagnoses during Period 1 be presented separately, and separately by arm. Only one set of SELECT-GCA data was presented, that for the placebo arm. The EAG assumes that this is new diagnoses during Period 1 and excludes conditions prevalent at baseline due to type 2 diabetes being 0%, but would be grateful if</i>	N/A	Response/clarification requested by the EAG during error check: The table provided in question A8 related to the ITT population and excluded prevalent conditions at baseline.	The EAG will revise the EAG report accordingly.

the company could confirm this at error check.'			

Issue 15 TA518 market survey

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report states: Page 17 <i>'The largely undocumented TA518 market survey suggests once per month'</i> Page 26 <i>'No details of the market survey method are presented in either the TA518 company submission or EAG report, with only the final resource use estimates being presented'</i> Page 143 <i>'Rates of resource use are taken from the TA518 company market survey, which is largely undocumented in TA518'</i>	Company requests amending the text to: <i>'The TA518 market survey, that was deemed appropriate by the TA518 EAG and committee, suggests once per month. However, no details of the market survey method are presented in either the TA518 company submission or EAG report'</i> <i>'No details of the market survey method are presented in either the TA518 company submission or EAG report, with only the final resource use estimates being presented. However, this was deemed appropriate by the TA518 EAG and committee'</i>	This can mischaracterise the acceptability of the data source, given that this source was accepted for decision-making by the EAG and the NICE committee in TA518.	No factual error. No revision required.

Page 172 <i>'The company relies upon the minimally documented TA518 market survey'</i> The wording in the report does not make clear that the market survey was accepted by NICE in TA518 which could be misleading.	<i>'Rates of resource use are taken from the TA518 company market survey, which presents no details of the methods in TA518, however this was deemed appropriate by the TA518 EAG and committee'</i> <i>'The company relies upon the minimally documented TA518 market survey, however, this was deemed appropriate by the TA518 EAG and committee'</i>		

Issue 16 Incidence of relapse

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 31 – The EAG report misrepresents the burden of relapses in GCA by incorrectly stating: <i>'Despite treatment, relapse rates remain high. A meta-analysis reported a 3.3% incidence of major relapse</i>	Company proposes the additional information to be added: <i>'Despite treatment, relapse rates remain high, with an estimated 50% of patients experiencing a relapse.'</i>^{10,11} and <i>'In the TOC STOP study, a cohort of relapsing and refractory GCA patients, relapses were shown to occur in 33% of patients after stopping tocilizumab,</i>	To avoid mischaracterising the burden of relapses in GCA. Highlighting only the proportion of major relapses in the new onset population does not reflect the full burden of relapses, specifically major relapses in the relapsed population, downplaying the unmet need.	Not a factual inaccuracy. The description clearly specifies the target population group and the type of relapse. However, additional information has now been included to further highlight the unmet need.

<i>in newly diagnosed patients.'</i>	<i>with 34% of these being major relapses</i> ¹²		

Issue 17 Positioning of upadacitinib

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 32 – The EAG report incorrectly states the positioning of upadacitinib: <i>'The company has positioned upadacitinib for use during the corticosteroid tapering phase in both newly diagnosed GCA patients and in patients with relapsing/refractory disease'</i>	Company requests the following amendment: <i>'The company has positioned upadacitinib for use during the corticosteroid tapering phase in adult patients with GCA'</i>	To accurately reflect the positioning of upadacitinib in the adult GCA population and ensure the language is aligned with the approved indication.	The EAG specifies the stages of the condition by using the terms <i>'newly diagnosed'</i> and <i>'relapse/refractory.'</i> However, it acknowledges that the specific age group (adults) was previously omitted and has now been included.

Issue 18 Methotrexate

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 43 – the EAG report contradictorily states: <i>'Firstly, the search terms for</i>	Company suggests removing the reference to methotrexate as it is later stated on page 46 of the EAG report <i>'the EAG agrees to company's</i>	To ensure consistency in the EAG reports commentary vis-à-vis Methotrexate	No factual error. It is reasonable to include broader search terms such as treatments that

<i>corticosteroids could be broadened to include search terms for Methotrexate'</i>	<i>rationale to exclude methotrexate from the treatment comparison'</i> and therefore contradicts the point on page 43.		are commonly used among the population of interest even if they are not formally included as comparator. For example, studies sharing similar methotrexate arms could be used to inform indirect comparisons between the intervention and comparators of interest.

Issue 19 SLR methodology for observational studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 43 – The EAG report states That the company included outcomes in the search strategy and highlighted this raises major concerns regarding the completeness of the search strategy. This phrasing could be misleading as it doesn't discuss the validity checks the company performed to ensure relevant studies were captured	The company request the following text is amended from: <i>'The EAG notes that since the decision problem does not restrict the population to being: at late stage, in remission, experiencing adverse effects or undergoing a tapering course of corticosteroids, restricting the search strategy in this way considerably reduces the sensitivity and increases the risk of removing potentially relevant studies. The EAG carried out a revised</i>	To aid clarity. The company acknowledges it is best practice to exclude outcome terms from the search strategy; however, the company ensured no relevant studies were missed by performing a validity check. In section 2.1.7 the EAG agrees with the company that the company's search strategy	This is not a factual inaccuracy. Although the EAG acknowledges that relevant studies were included, the discrepancy in the total number of records after deduplication (1,559 versus 1,831) raises concern. Additionally, the EAG's search did

	<i>search that did not include these terms (see Appendix 1: EAG searches. Appendix 1: EAG searches), which retrieved 1831 de-duplicated results. This raises major concerns regarding the completeness of the search strategy. This is further discussed in Section 2.1.7'</i> To: <i>"The EAG notes that since the decision problem does not restrict the population to being: at late stage, in remission, experiencing adverse effects or undergoing a tapering course of corticosteroids, restricting the search strategy in this way considerably reduces the sensitivity and increases the risk of removing potentially relevant studies. Nevertheless, the company performed a validity check to ensure no relevant studies were missed. This validity check consisted in conducting backwards citation searches using relevant systematic literature reviews and meta-analyses identified through the database searches. The EAG carried out a</i>	was methodologically accurate and comprehensive	not retrieve the studies included in the SLR. These discrepancies highlight potential gaps in the review process.

	<i>revised search that did not include these terms (see Appendix 1: EAG searches. Appendix 1: EAG searches), which retrieved 1831 de-duplicated results. This is further discussed in Section 2.1.7'</i>		
Page 44 the EAG report states that the company didn't provide justification for the narrowed focus on specific outcomes, raising concerns about potential exclusion of relevant studies. This text can be misleading.	The company requests the following text is amended from: <i>'The company didn't provide justification to for the narrowed focus on specific outcomes which raises concern to the EAG about potential exclusion of relevant studies.'</i> To <i>'The company didn't provide justification to for the narrowed focus on specific outcomes which raises concern to the EAG about potential exclusion of relevant studies.</i> Nevertheless, it is important to acknowledge that the SELECT-GCA trial had an extensive and robust list of endpoints that are widely used in GCA trials'	To aid clarity. It is important to highlight that the SELECT-GCA trial outcomes are widely representative of what is used in GCA trials.	This is not a factual inaccuracy. EAG's statement was concerned with criteria for selecting studies into the SLR, not the specific outcomes used in the SELECT-GCA.

Page 45 – the EAG report incorrectly report states: <i>‘However, the company did not explicitly describe the methodology used to identify these 37 additional reports which raised concern to the EAG regarding the transparency of the selection process’</i>	This statement should be removed or amended to reflect the additional details provided during clarification questions, which were: <i>‘To identify the subset of observational studies meeting PICOS criteria that report corticosteroid-related AEs, full-text records of observational studies meeting PICOS criteria were reviewed by two independent researchers to determine whether any corticosteroid-related AE data were present. Disagreements between researchers were resolved by discussion or by review with a third researcher. An observational study was not selected for extraction of adverse event data if researchers agreed that corticosteroid-related AE data were not reported’</i>	Correction of a factual inaccuracy	This is not a factual inaccuracy. CS Appendix B specifically reported methodology for identifying RCTs. However, the methodology used to identify the 37 observational studies was not clearly outlined and the PRISMA diagram does not include information regarding the source of those studies.

Issue 20 Model update implemented at clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response

Page 147 the EAG report states: <i>'The EAG has not been able to replicate these estimates due to the model changes not having been documented and would be grateful if the company could provide further details at factual accuracy check'. This statement is not accurate</i>	AbbVie request this statement is removed or amended.	The details of these model changes were reported in either the company response document or in the appendices. However, in an attempt to add further clarification, each of the model changes will be outlined below. In both Trace_tx1 and Trace_tx2 column CO was updated due to the clarification questions B8 and B9. The change to the formulae in these columns was to replace the existing formulae to : =INDEX(\$P\$20:\$Z\$72, MATCH(0,\$O\$20:\$O\$72,0), MATCH(MAX(IF(Effectiveness!\$F\$85="Yes",20,0),NUMBERVALUE(IFERROR(((INDEX(\$P\$19:\$Z\$19,MATCH(CN21,\$P\$19:\$Z\$19,-1))*AC21*(1-\$J21)*\$K21*(1-\$M21)) + (IF(Effectiveness!\$F\$75>(INDEX(\$P\$19:\$Z\$19,(MATCH(CN21,\$P\$19:\$Z\$19,-1))))),Effectiveness!\$F\$75,(INDEX(\$P\$19:\$Z\$19,(MATCH(CN21,\$P\$19:\$Z\$19,-1)))))*AC21*(1-\$J21)*\$K21*\$M21) + ((INDEX(\$P\$19:\$Z\$19,MATCH(ES21,\$P\$19:\$Z\$19,-1))*SUM(\$AH21:\$CG21)*\$L21*(1-\$I21)*(1-\$M21)) + (IF(Effectiveness!\$F\$75>((INDEX(\$P\$19:\$Z\$19,(MATCH(ES21,\$P\$19:\$Z\$19,-1))))),Effectiveness!\$F\$75,((INDEX(\$P\$19:\$Z\$19,(MATCH(ES21,\$P\$19:\$Z\$19,-1)))))*SUM(\$AH21:\$CG21)*\$L21*(1-\$I21)*\$M21) + ((INDEX(\$P\$19:\$Z\$19,(MATCH(ES21,\$P\$19:\$Z\$19,-1))*CH21*(1-\$J21)*\$L21*(1-\$M21)))) +	Despite the additional information the EAG has still not been able to replicate the revised company model. It also appears that not all model changes have been documented; e.g. setting the principal diagonal from CS25 values all to zero. The EAG will add text to the effect that it still has not managed to replicate the revised company analysis, and that it thinks the model revisions merely shift the

as details were provided during CQs.		(IF(Effectiveness!\$F\$75>((INDEX(\$P\$19:\$Z\$19,(MATCH(ES21,\$P\$19:\$Z\$19,-1))))),Effectiveness!\$F\$75,((INDEX(\$P\$19:\$Z\$19,(MATCH(ES21,\$P\$19:\$Z\$19,-1)))))*CH21*(1-\$J21)*\$L21*\$M21)) /SUM(AC21*(1-\$J21)*\$K21, SUM(\$AH21:\$CG21)*\$L21*(1-\$I21),(CH21*(1-\$J21)*\$L21),0)), \$P\$19:\$Z\$19,-1)) Please note that this formula was taken from Trace_tx1 CO22 and that the formulae for the other cells in that column would have different cell references due to needing to pull in data from other rows. However, coping this formula into cell CO22 and then dragging the formula into the rest of the column would result in its successful implementation. In response to clarification question B13 a check was conducted of all NHS reference costs within the model and updates were undertaken. These updates were outlined in appendix B13 and affect the following cells in the model: Raw_HCRU C11, Raw_Safety F140, F141, F147, F148 and F151.	problem elsewhere; i.e. the average dose in first week of flare was previously correctly calculated but the revisions mean that this is no longer the case. The EAG thinks the more natural correction is for column CS to drop down to the next available steroid dose rather than jump up to the next higher dose. The EAG will delete the sentence asking for further clarification on this issue during FAC.

Issue 21 Duration of transient conditions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 171 the EAG report states: <i>‘This implicitly assumes that the durations of these conditions’ quality of life effects is one year’.</i> This is factually inaccurate as disutilities applied do not represent annual QALY losses.	Remove the paragraph beginning ‘The quality-of-life decrements for transient conditions...’ and the subsequent passage that assigns one- and six-month durations. Replace them with the following clarification: <i>‘In the economic model the disutility for every transient condition is applied once, in the weekly cycle in which the event occurs. The published utilities used as inputs are cross-sectional point estimates and do not represent annual QALY losses; consequently, no scaling for duration is required.’</i>	The text is factually inaccurate. Deleting the proposed duration adjustments corrects the factual error that disutilities had been applied for a full year. Retaining the amendment would divide some decrements by up to 52 and distort incremental QALY calculations. The replacement wording makes the modelling approach transparent and preserves alignment with standard health-economic practice for acute events in a weekly Markov framework.	No factual error. No revision required. The company has withdrawn this as an issue.

Issue 22 Figure and table errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Figures and tables in the EAG report do not include an abbreviations list.	The company suggest including abbreviations below each figure and table, as appropriate.	To aid clarity.	EAG do not consider this necessary as the meaning for most abbreviations in tables and figures is obvious and a list of abbreviations is provided at the beginning of the report.
Page 60, Figure 2 The number of subjects at risk does not align with the colour key indicated on the figure	Company requests that the graph be redrawn to accurately reflect the data	Factual inaccuracy.	Thank you. The EAG has redrawn the figure and replaced the old figure.
Page 67, Table 9 Table heading includes ' <i>upadac</i> '	Company proposes that the additional ' <i>upadac</i> ' in the heading row be removed to avoid confusion	Formatting amendment for clarity.	EAG accepts the proposed amendment.
Page 71, Figure 13	Company requests that the figure be amended to show up to 30 years to align with the other figures of the report	Formatting amendment for clarity.	Not a factual inaccuracy. EAG considers 20 years

Axis only extends to 20 years			being sufficient in this case.
Page 72, Figure 15 Title is mislabelled.	Company requests the figure title be corrected to: <i>'Weibull, exponential, Chen, and Rayleigh models for new-onset GCA'.</i>	To aid accurate interpretation of the graph.	EAG has revised the title to read "Parametric models for new onset GCA. Upper panel Weibull and exponential models; lower panel Chen and Rayleigh models"
Page 79, Figure 19 Legend label for lognormal upadacitinib is ' <i>Inupa</i> ' and does not follow the formatting of other labels.	Company requests that the legend label for lognormal upadacitinib be updated to: <i>In upad</i> '.	To aid clarity and avoid confusion.	EAG has accepted the amendment.
Page 80, Figure 21 and Figure 22 Figure titles state ' <i>extrapolated to 30 years</i> ' but the axis only show up to 10 years	Company requests that the graph be corrected to show to 30 years.	For coherence.	EAG has corrected the titles for Figure 21 and Figure 22 to indicate the extrapolation was to 10 years.

Page 85, Figure 27, Page 105, Figure 40 Figure title refers to '<i>Select GA</i>'	Company requests that this be corrected to: 'SELECT-GCA'.	Inaccuracy.	EAG accepted the amendment.
Page 85 Cross reference to Figure 23 does not work, and appears to refer to the incorrect figure	Company proposes that this cross reference be updated to: 'Figure 28'	Inaccuracy in cross-referencing.	Thank you. EAG has updated the cross-reference.
Page 87, Figure 28 The lognormal figure has additional unlabelled lines.	Company proposes that this figure be corrected by removing the additional lines or relabelling.	To aid clarity.	EAG has revised the figure caption and added footnotes to label different lines in the figure.
Page 113 The cross-reference to Table 42 has linked to a section of text which has incorrectly been copied across.	Company proposes that error be amended.	To avoid confusion.	EAG accepts the proposed amendment.

Issue 23 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
As a general comment, the EAG report contains numerous typographical and grammatical errors and poorly structured sentences. Some of these are listed below but note this is not an exhaustive list.	The company suggests a thorough proofread and copy edit to remove these errors and improve clarity and understanding.	To avoid any misinterpretation and ambiguity.	EAG has further proofread the report and corrected the typographical errors. As a general comment, the EAG remarks that the very late arrival of the company's corrected KM data necessitated extensive and fast adjustment of the EAG report; consequently, the EAG had a great time constraint to undertake its proof-reading.
Page 19, Section 1.3 Spelling mistake ' <i>patients with new on-set GCA</i> '	Company proposes that this be corrected to: 'patients with new-onset GCA'	Typographical error	The EAG accepts the amendment.
Page 30, Section 1.2.1 Spelling mistake GCA is	Company proposes that this be corrected to: 'GCA'	Typographical error	The EAG accepts the amendment.

incorrectly referred to as 'CGA'			
Page 30, Section 1.2.1 Spelling mistake ' <i>The extra cranial GCA</i> '	Company requests that this be corrected to: 'The extracranial GCA'	Typographical error	The EAG accepts the amendment.
Page 30, Section 1.2.1 The text ' <i>Relapse</i> ^{10,11,13-15} ' is included without further context	Company proposes this text be removed	Typographical error	The EAG accepts the amendment.
Page 32, Section 1.2.2 The word 'acceptability' is used incorrectly in the sentence ' <i>However, challenges remain regarding its accessibility particularly beyond major treatment centres, acceptability among elderly patients</i> '.	Company proposes this be amended to: 'However, challenges remain regarding its accessibility particularly beyond major treatment centres, especially among elderly patients'	Typographical error	The use of the word 'acceptability' was not an error. The issue was highlighted by the EAG's clinical advisor. The text was revised to read '...', and acceptability among elderly patients'.
Page 32, Section 1.2.2 The word ' <i>effective</i> ' is used incorrectly; 'As it can take	Company proposes this be amended to: 'effect'	Typographical error	The EAG accepts the amendment.

several weeks or months for tocilizumab to take effective,’			
Page 44, Section 2.1.1 The text ‘ <i>Appendix 1: EAG searches</i> ’ is duplicated	Company suggests removing the duplicated reference to Appendix 1	Typographical error	The EAG accepts the amendment.
Page 44, Section 2.1.1 Spelling mistake a period and space is missing between two sentences	Company suggests adding the missing period and space between sentences	Typographical error	The EAG accepts the amendment.
Page 47, Section 2.1.6 Spelling mistake ‘associated with cortico-steroids use’	Company suggests amending to: ‘associated with corticosteroid use’	Typographical error	The EAG accepts the amendment.
Page 47, Section 2.1.6 Incorrect use of the word ‘and’ in ‘ <i>this RWE study and not listed</i> ’	Company proposes this be amended to: ‘this RWE study was not listed’	Typographical error	The EAG accepts the amendment.

Page 52 Spelling mistake ' <i>The secondary end point</i> '	Company suggests this is corrected to: '<i>The secondary endpoint</i>'	Typographical error	The EAG accepts the amendment.
Page 65 Text refers to ' <i>clinic advice</i> '	Company proposes that this be amended to '<i>clinical advice</i>'	Typographical error	The EAG accepts the amendment.
Page 67 Additional period; ' <i>The KM plot 95% CIs.overlap</i> '	Company suggests that the additional period between ' <i>CIs</i> ' and ' <i>overlap</i> ' is removed	Typographical error	The EAG accepts the amendment.
Page 70 Spelling mistake ' <i>upadacitinib</i> '	Company suggests amending the spelling to: '<i>upadacitinib</i>'	Typographical error	The EAG accepts that there is an amendment needed. Previously it was ' <i>upadacitiinib</i> ' which is corrected to ' <i>upadacitinib</i> '

Page 81 Spelling mistake ' <i>He AbbVie PBO</i> '	Company suggests correcting this to: '<i>The AbbVie PBO</i>'	Typographical error	The EAG accepts the amendment.
Page 82, Section 2.5.1.6 Spelling mistake ' <i>therefor</i> '	Company suggests that this is corrected to: '<i>therefore</i>'	Typographical error	The EAG accepts the amendment.
Page 106, Section 2.6 Missing word ' <i>arm</i> ' when describing upadacitinib results	Company proposes to amend to: 'higher in the upadacitinib <i>arm</i>'	Typographical error	The EAG accepts the amendment.
Page 111 Spelling mistake 'Gomperts'	Company proposes this be amended to: '<i>Gompertz</i>'	Typographical error	The EAG accepts the amendment.

Location of incorrect marking	Description of incorrect marking	Amended marking
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.

(Please add further lines to the table as necessary)

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