National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Upadacitinib for treating giant cell arteritis [ID6299]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	AbbVie	AbbVie consider it appropriate to refer this topic to NICE for appraisal.	Thank you for your comment. No action required.
	British Society of Rheumatology	A STA is very welcome this is an area of significant unmet need with only one currently available steroid sparing agent viaTA518, and that with a time-limit of 12 months, even in the face of relapse. Clinicians may be caught between using a JAK inhibitor which may have thromboembolic risk in the elderly (the target demographic) and tocilizumab 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) and whether MTAC might be more appropriate. 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.	Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme as a single technology appraisal. No action required. In TA518, the company's model applied 12 month stopping rule and assumed people would

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		It is important to emphasise that relapse rates in GCA can be >40% and so treatments other than steroids are very much needed**.**	only have a single course of treatment. The purpose of the appraisal will be to determine whether upadacitinib is a cost effective treatment option within its marketing authorisation. It is anticipated that tocilizumab may be a comparator for people with relapsed or refractory giant cell arteritis. Reconsideration of the recommendations for tocilizumab are outside of the remit for this appraisal.
	Royal College of Ophthalmologists	Single Health Technology Evaluation is appropriate.	Thank you for your comment. No action required
	NHS England Specialised Commissioning	There is enormous unmet need for people with GCA. This disease exclusively affects an older population (mean age 77) and requires high-dose glucocorticoids for many years, frequently for over a decade.	Thank you for your comment. Comments noted. NICE has scheduled this topic into

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		High-dose glucocorticoid treatment leads to numerous side-effects that have significant costs to the NHS, including infections, fracture (manuscript in preparation), diabetes, hypertension, cardiovascular events and increased mortality. The impact of glucocorticoids on change in body habitus, mental health, sleep disturbance, sarcopenia and vision (glaucoma and cataracts) are primary concerns for patients and have major impacts on quality of life. Access to tocilizumab (TA518) has been transformational for many patients, with most patients flaring on treatment discontinuation. There is no clinical trial evidence that conventional DMARDs substantially reduce glucocorticoid requirements or modify the pathogenic processes in GCA. The TOC-STOP study found no evidence that DMARDs prolonged the time to flare after tocilizumab discontinuation. There is a high burden of cardiovascular disease and cardiovascular risk factors in GCA patients by virtue of the age of this population. Our recent study, demonstrated age was strongly associated with ischaemic complications at presentation and anti-coagulant use (for other indications) at baseline reduced the risk of ischaemic complications. These data together with recent international genetic studies highlight the need to reappraise the role of thrombosis in GCA pathogenesis. Whilst the clinical community welcome access to a greater number of therapies for GCA, there is some concern we may be required to use a drug with an increased risk of thromboembolic disease ahead of tocilizumab, which is now available as a biosimilar, well tolerated and clinically effective in many GCA patients. Most GCA patients stop glucocorticoids completely once established on tocilizumab therapy, with reduced primary and secondary care appointments that would otherwise be required to monitor glucocorticoid adverse events.	its work programme. The evaluation will consider current clinical management of GCA without upadacitinib. .

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		Not all GCA patients respond to or tolerate tocilizumab and so there remains an unmet need for alternative therapies. Evaluation of upadacitinib use in GCA via STA would be a most welcome development. However, there is also a pressing need to review the extended use of tocilizumab beyond 12 months, as relapse after cessation of the currently funded 12-month treatment course per lifetime (TA518) occurs in up to 50% of patients where one third of relapses are EULAR-defined major relapse [Quick 2024]. These data on relapse rates are consistent with the GiACTA clinical trial [Stone 2021] and single centre observational studies [Matza 2023, Samec 2023]. These relapsing patients have no option but to return to glucocorticoids with their resulting toxicity, as conventional DMARDs are of limited or unproven benefit. When the patient had tolerated and responded well to tocilizumab, it makes little sense to be forced to swap to UPA, a (potentially more expensive) drug with which we have limited experience, where there are concerns regarding thromboembolic risk in the older population affected. Therefore, an MTA of both upadacitinib and tocilizumab would be most appropriate. References: Quick V, Abusalameh M, Ahmed S, Alkoky H, Bukhari M, Carter S, et al. 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.	

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		Stone JH, Han J et. al. Long-term effect of tocilizumab in patients with giant cell arteritis: open-label extension phase of the Giant Cell Arteritis Actemra (GiACTA) trial. Lancet Rheumatology 2021; 3:e328-e336. Matza MA, Dagincourt N, et. al. Outcomes during and after long-term Tocilizumab treatment in patients with giant cell arteritis. RMD Open 2023; 9:e002923. Samec MJ, Rakholiya J, et. al. Relapse risk and safety of long-term Tocilizumab use among patients with giant cell arteritis: A single-enterprise cohort study. J Rheumatol 2023; 50:1310-1317.	
Wording	AbbVie	AbbVie has no comments on the suggested remit as the remit covers the anticipated licensed indication. The license wording is anticipated to be: [redacted]	Thank you for your comment. No action required.
	British Society of Rheumatology	As above, why is NICE considering only Upadacitinib and not concurrently reviewing the appropriateness of the current tocilizumab guidance TA518, that tocilizumab therapy can't be given if a patient has already had 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.	Thank you for your comment. Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme as a single technology appraisal. TA 518, recommends

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			tocilizumab for use in the NHS. The evaluation will consider current clinical management of GCA without upadacitinib.
	Royal College of Ophthalmologists	No alternative suggestion.	Thank you for your comment. No action required
	NHS England Specialised Commissioning	There is an urgent need to reappraise TA518 from the perspective of use at disease outset and repeat courses for patients who respond and flare on treatment discontinuation. Upadacitinib may be best considered as a second-line treatment to tocilizumab unless there are contra-indications, adverse events or non-response, or alternatively the patient is unable to administer subcutaneous injections.	Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme. Reconsideration of the recommendations for tocilizumab are outside of the remit for this appraisal.
Timing Issues	AbbVie	The main treatment option to manage giant cell arteritis (GCA) are corticosteroids, however cumulative corticosteroid dose exposure are associated with a risk of adverse events and toxicity. Currently there is only one licenced targeted treatment option for patients, tocilizumab, which is recommended in the relapsed population only, with a treatment duration limited to one year. Despite these current treatment options, relapse rates remain high for patients, with one third of patients relapsing within one year of stopping tocilizumab, and almost half of patients	Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme. No action required.

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		relapsing by two years.1 As such there remains a significant unmet need for patients with GCA.	
	British Society of Rheumatology	In terms of urgency, this single TA is urgently needed for the cohort of patients who have relapsed following tocilizumab cessation. There is currently a group of patients with relapsing GCA who have no good treatment options other than long-term corticosteroids, mainly due to the stipulations of NICE TA518. These patients are now subject to a postcode lottery dependent on application of individual cases for hospital / Trust based funding.	Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme. No action required. The evaluation will consider current clinical management of GCA without upadacitinib.
	Royal College of Ophthalmologists	This is a timely evaluation, given the randomised control trial data.	Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme. No action required.
	NHS England Specialised Commissioning	There is an urgent need for access to glucocorticoid-sparing therapies for GCA. We would not prioritise this above the reappraisal of TA518. There is a pressing unmet need for less toxic more effective treatment for GCA patients that relapse after completion their lifetime allocation of tocilizumab, or those where tocilizumab is contraindicated, poorly tolerated, or ineffective.	Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme. No action required. Reconsideration of the recommendations for tocilizumab are outside

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			of the remit for this appraisal.
Additional comments on the draft remit	AbbVie	NA	No action required.
	British Society of Rheumatology	NA	No action required.
	Royal College of Ophthalmologists	None	No action required.
	NHS England Specialised Commissioning	NA	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AbbVie	AbbVie suggests that where treatment options are detailed in the background information, it should be noted that due to the patient demographic of GCA a proportion patients would be considered high risk or contraindicated to corticosteroids, limiting their options or leading to suboptimal management.[2] Additionally, there is uncertainty in the corticosteroid tapering period, and clinical practice may reflect faster tapering as per the BSR/EULAR guidelines. Furthermore, while some patients are treated with methotrexate, this use is unlicensed and likely due to the limited treatment options available for patients, with little clinical data to support its use. Finally, whilst	Thank you for your comment. The scope has been updated with some suggested changes. The aim of the background is to provide a very brief summary of the disease area. Further details can be included in all submissions for this evaluation for consideration by the

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		tocilizumab is recommended by NICE for relapsing GCA patients, it should be added that it is limited to a one-year treatment duration. Where the nature of GCA disease is being described, we believe it should be highlighted that it is a chronic condition.	appraisal committee. Methotrexate has been added as a comparator because although unlicensed it is in use in NHS clinical practice. The treatment duration of tocilizumab covered by NICE recommendations in TA518 has been added to the background section of the scope
	British Society of Rheumatology	The background appears to have derived from literature that is perhaps 20 years old. GCA affects far more than the head and neck; it should not be called temporal arteritis; there is no literature around previous cardiovascular disease being a risk factor; and the complications need to be broken down into immediate and late and need to recognise the contribution of steroids to the late complications. Lingual necrosis also needs to be recognised. The incidence data is old and deeply flawed. There are newer data available. The background information is therefore incomplete. The description of NICE TA518 does not fully represent the current situation for patients with relapsing GCA (which is about half of the total GCA population). NICE TA518 clearly states one of the conditions for prescribing tocilizumab: “tocilizumab is stopped after 1 year of uninterrupted	Thank you for your comment. The scope has been updated with some suggested changes. The aim of the background is to provide a very brief summary of the disease area. Further details can be included in all submissions for this evaluation.

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		treatment at most". Together with the stipulation "if they have not already had tocilizumab", this means there are currently many patients who have been successfully treated with tocilizumab for 1 year but have had to stop tocilizumab after the stipulated 1 year and have relapsed again. As they are not allowed any further tocilizumab, there are currently no good treatment options for this patient group except for corticosteroids, which are very toxic in the long term. **Ref:** [Quick V, Abusalameh M, Ahmed S, Alkoky H, Bukhari M, Carter S, Coath FL, Davidson B, Doddamani P, Dubey S, Ducker G, Griffiths B, Gullick N, Heaney J, Holloway A, Htut EEP, Hughes M, Irvine H, Kinder A, Kurshid A, Lim J, Ludwig DR, Malik M, Mercer L, Mulhearn B, Nair JR, Patel R, Robson J, Saha P, Tansley S; TOC STOP 2022 Investigators; Mackie SL. 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.]	
	Royal College of Ophthalmologists	The burden of prolonged use of glucocorticoids in this patient group is under estimated. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum. 2003 Oct 15;49(5):703-8 - Adverse events associated with GCs were recorded in 86% patients and 2 or more events occurred in 58%. Long-term relapse and complications need to be highlighted.	Thank you for your comment. The scope has been updated to state the burden of prolonged use of corticosteroids and the relapse rate.

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		Pipitone N, Boiardi L, Bajocchi G, Salvarani C. Long-term outcome of giant cell arteritis. Clin Exp Rheumatol. 2006 Mar-Apr;24(2 Suppl 41):S65-70. PMID: 16859599	
	NHS England Specialised Commissioning	The background information is somewhat out of date and incomplete. It does not reflect the spectrum nor burden of disease currently seen in the UK, particularly the large vessel variant of GCA that occurs at a much earlier age and can lead to critical limb ischaemia, aortic dissection, aortic thrombosis and aortic aneurysm formation. The background does not convey the magnitude of side-effects related to glucocorticoids. This should indicate that side-effects are virtually universal and are associated with increased mortality. These include infections, cataracts, glaucoma, hypertension, T2DM, osteoporosis (with increased fracture risk), osteonecrosis, increased risk of cardiovascular events including thromboses, adrenal insufficiency mental health disturbances and sarcopenia amongst others. This has major cost and resource implications for health care services. Would be important to include some information about relapse and refractory states e.g. frequency as this is potentially a subpopulation as per the tocilizumab implementation. The cited background information references are a single BMJ article and a patient information leaflet. There is now considerable evidence that GCA is a relapsing and often chronic disease in many patients, where substantial glucocorticoid (“steroid”) toxicity is seen in almost all patients.	Thank you for your comment. The scope has been updated with some suggested changes. The aim of the background is to provide a very brief summary of the disease area. Further details can be included in all submissions for this evaluation for consideration by the appraisal committee

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		Relapse is seen in approximately 50% of GCA patients. One third of patients have multiple relapses. High relapse rates translate into extended treatment in many cases [Moreel 2023]. There is no compelling evidence that any conventional DMARD such as methotrexate, or tocilizumab are disease modifying because clinical relapse rates and doses required to treat relapse return to pre-DMRAD rates once the DMARD is stopped [Quick 2024]. Duration of steroid treatment in GCA is not 18-24 months. The 2020 BSR GCA guidelines suggest attempting to taper over 12-18 months providing there is no relapse (return of GCA symptoms, signs or laboratory markers of inflammation) [Mackie 2020]. However, observational data suggest that most patients have to remain on steroids much longer than recommended, with a mean treatment duration exceeding two years. Steroid treatment is generally required for 1-3 years, with a substantial minority (approximately 25-40% depending on the cohort studied) needing treatment for over 5 years [see illustrative selection of references 3-7]. The background should convey the significance of the side-effects related to prednisolone. This should indicate that side-effects with prednisolone are virtually universal and should include a much more comprehensive list of all the numerous side effects specified by OMERACT such as cataracts, hypertension, T2DM, osteoporosis (with increased fracture risk), increased risk of cardiovascular events, and mental health disturbances. This has cost and resource implications for health care services. The morbidities included (vision loss, stroke and aortic aneurysm) are permanent damage outcomes only. Morbidity from active disease should	

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		also be considered including headache, PMR related musculoskeletal pain, joint and muscle stiffness, fatigue, sleep disturbance, weight loss, depression and anxiety. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. This horizon needs to be beyond the GiACTA and SELECT-GCA trial period to take into account the protracted steroid treatment needed by most patients. There is no evidence yet that Upadacitinib is disease modifying and GCA is a chronic relapsing disease in many. It should therefore be assumed that relapse rate and steroid requirement will return to the pre-UPA rate as per observational studies of steroid monotherapy [Moreel 2023] and observational studies of tocilizumab [Quick 2024]. References: 1. Moreel L, Betrains A, Molenberghs G, Vanderschueren S, Blockmans D. Epidemiology and predictors of relapse in giant cell arteritis: A systematic review and meta-analysis. Joint Bone Spine. 2023 Jan;90(1):105494. 2. Mackie SL, Dejaco C, Appenzeller S, Camellino D, Duftner C, Gonzalez-Chiappeet S, et al, British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis, Rheumatology, Volume 59, Issue 3, March 2020, Pages e1–e23. 3. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum. 2003;49(5):703-8 4. Lai LYH, Harris E, West RM, Baxter PD, Scott DL, Helliwell T. Association between glucocorticoid therapy and incidence of diabetes	

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		mellitus in polymyalgia rheumatica and giant cell arteritis: a systematic review and meta-analysis. RMD Open. 2018;4(1):e000521. 5. Restuccia G, Boiardi L, Cavazza A, Catanoso M, Macchioni P, Muratore F, et al. Flares in biopsy-proven giant cell arteritis in northern Italy: characteristics and predictors in a long-term follow-up study. Medicine (Baltimore). 2016;95(9):e3524. 6. Labarca C, Koster MJ, Crowson CS, Makol A, Ytterberg SR, Matteson EL, et al. Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: a retrospective cohort study. Rheumatology (Oxford). 2016;55(2):347-56. 7. Hachulla E, Boivin V, Pasturel-Michon U, Fauchais AL, Bouroz-Joly J, Perez-Cousin M, et al. Prognostic factors and long-term evolution in a cohort of 133 patients with giant cell arteritis. Clin Exp Rheumatol. 2001;19(2):171 8. Alba MA, Kermani TA, Unizony SH, Gribbons KB, Pipitone N, Warrington KJ, et al. Relapses in giant cell arteritis: Updated review for clinical practice. Autoimmun Rev. 2024;23(1):103580.	
Population	AbbVie	AbbVie recommends the population be defined as adult patients with giant cell arteritis.	Thank you for your comment. The scope has been updated with the suggested change.
	British Society of Rheumatology	Generally, yes, but there is no definition beyond ‘people with giant cell arteritis’. We would probably clarify this as ‘people with objective evidence of giant cell arteritis on either imaging or biopsy’.	Thank you for your comment. No action required, the appraisal will be carried out in the population as defined in

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			the marketing authorisation.
	Royal College of Ophthalmologists	Yes, people living with giant cell arteritis.	Thank you for your comment. No action required.
	NHS England Specialised Commissioning	We propose patients with a confirmed diagnosis (histological or imaging) unless there is MDT agreement that GCA is the most likely diagnosis in the absence of confirmatory tests. The latter is particularly important to avoid discriminating against people whose disease developed during the COVID-19 pandemic when there was limited access to confirmatory diagnostics. It is not clear whether the population described is all people or just those with first episode of GCA e,g, not relapsing patients	Thank you for your comment. No action required, the appraisal will be carried out in the population as defined in the marketing authorisation
Subgroups	AbbVie	The following subgroups could be considered to be distinct due to differing treatment options and outcomes: Patients with newly diagnosed giant cell arteritis Patients with relapsing giant cell arteritis.	Thank you for your comment. The scope has been updated with the suggested changes.
	British Society of Rheumatology	Patients who have experienced glucocorticoid (=corticosteroid) toxicity are at high risk of future glucocorticoid toxicity, and the technology would 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. **Ref** Lyne SA, Yip K, Vasiliou VS, Katz DA, Richards P, Tieu J, Black RJ, Bridgewater S, Palmowski A, Beaton D, Maxwell LJ, Robson JC, Mackie SL, Goodman SM, Hill CL. Consensus of the definitions of the	Thank you for your comment. This subgroup subgroup has been added to the scope. If evidence allows, other subgroups not listed in the scope should be presented in evidence submission

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		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.	for the committee to consider.
	Royal College of Ophthalmologists	• Yes, those with relapsing disease • Yes, those who may be intolerant of high dose glucocorticoids	Thank you for your comment. Subgroups have been added to the scope. If evidence allows, other subgroups not listed in the scope should be presented in evidence submission for the committee to consider
	NHS England Specialised Commissioning	Without access to the clinical trial data, it is not possible to comment on subgroups in detail. The burden of glucocorticoid toxicity is so large this should be considered for all GCA patients with active disease requiring high-dose glucocorticoids for example: 1. Newly-diagnosed patients with GCA 2. Patients with relapsing or refractory disease requiring, for example, >10mg prednisolone 3. Patients with relapsing or refractory disease who do not respond adequately to tocilizumab, experience AEs with tocilizumab or where tocilizumab is contra-indicated	Thank you for your comment. Subgroups have been added to the scope. If evidence allows, other subgroups not listed in the scope should be presented in evidence submission for the committee to consider

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		4. Patients with relapsing disease after completion of 12 months treatment with Tocilizumab 5. Patients who have developed steroid toxicity or have pre-existing comorbidities likely to be exacerbated by steroids (e.g. diabetes, HT, osteoporosis, neuropsychiatric illness, obesity).	
Comparators	AbbVie	All relevant comparators have been included. It should be noted tocilizumab is given alongside a 26-week steroid taper.	Thank you for your comment. Comment noted.
	British Society of Rheumatology	The comparator is currently tocilizumab for 12m duration only, which needs to be made explicit. Methotrexate is an alternative comparator as it is listed in the British Society for Rheumatology Guideline on diagnosis and treatment of giant cell arteritis: Rheumatology, Volume 59, Issue 3, March 2020, Pages 487–494, https://doi.org/10.1093/rheumatology/kez664). Methotrexate does not have marketing authorisation for GCA as it is a generic drug, but nonetheless it is widely used.	Thank you for your comment. Comment noted. It is anticipated that more information regarding relevant treatments will be included in the submissions. Methotrexate in combination with a tapered dose of corticosteroids has been added as a comparator.
	Royal College of Ophthalmologists	They have not stated methotrexate as a comparator.	Thank you for your comment. Methotrexate in

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			combination with a tapered dose of corticosteroids has been added as a comparator.
	NHS England Specialised Commissioning	No, as in clinical practice if TCZ is indicated but contraindicated then methotrexate might be used The only comparators with clinical trial data are glucocorticoid monotherapy and tocilizumab in combination with medium-term glucocorticoids. DMARDs, including methotrexate, do not prevent flares on tocilizumab withdrawal and so should not be considered as an alternative treatment. The comparators should include: • Tapering course of steroid • 12 months Tocilizumab with a tapering course of steroids (in people with relapsing or refractory disease) Methotrexate is listed as a treatment option in the 2020 BSR GCA Guidelines, but RCT evidence (which is limited to new onset disease) suggests the benefit is limited. It and other conventional DMARDs only tend to be used in routine practice when the patient is not able to have the effective steroid sparing alterative tocilizumab (for funding or clinical reasons). In the TOC STOP study [Quick 2024], 43.2% patients were co-prescribed a csDMARD during the last three months of weekly Tocilizumab and 53.3% were taking a csDMARD within four weeks of weekly Tocilizumab cessation. There was no relationship between time to GCA relapse and	Thank you for your comment. Methotrexate in combination with a tapered dose of corticosteroids has been added as a comparator.

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		csDMARD use, demonstrating lack of disease-modifying efficacy in relapsing patients.	
Outcomes	AbbVie	In addition to the mentioned outcomes, please also include cumulative dose of corticosteroids.	Thank you for your comment. Although it is anticipated that adverse effects of long-term corticosteroid use will capture health outcomes across the dose range of corticosteroids included in the model, cumulative dose of corticosteroids has been added as a separate outcome to specifically assess the extent to which upadacitinib is corticosteroid sparing.
	British Society of Rheumatology	The chosen outcomes do not fully reflect what is important about steroid sparing therapies in GCA. The adverse effects of long-term glucocorticoid treatment should reflect all the core domains specified by OMERACT. 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. Consider also capturing:	Thank you for your comment. Although it is anticipated that adverse effects of long term corticosteroid use will capture health outcomes across the dose range of corticosteroids included

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		• Glucocorticoid dose required to control disease activity. • Cumulative glucocorticoid dose. • Impact of glucocorticoids on patients' lives. • Impact of giant cell arteritis on patients' lives. It is essential to consider the mental-health sequelae of the disease itself as well as the glucocorticoid therapy. It would also be useful to consider and define the relapse rates of different treatments and at given time intervals – e.g.12 and 24 months. **References:** Lyne SA, Yip K, Vasiliou VS, Katz DA, Richards P, Tieu J, Black RJ, Bridgewater S, Palmowski A, Beaton D, Maxwell LJ, Robson JC, Mackie SL, Goodman SM, Hill CL. 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. Robson JC, Almeida C, Dawson J, Bromhead A, Dures E, Guly C, Hoon E, Mackie S, Ndosi M, Pauling J, Hill C. 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:	in the model, cumulative dose of corticosteroids has been added as a separate outcome to specifically assess the extent to which Upadacitinib is corticosteroid sparing. It is anticipated that the impact of corticosteroids and giant cell arteritis will be captured within health related quality of life. Time to relapse after disease remission is included as an outcome. Please note that the list of outcomes listed in the scope are not intended to be exhaustive and the appraisal committee can consider further

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		10.1093/rheumatology/keab076. PMID: 33528002; PMCID: PMC8487303.	outcomes where relevant.
	Royal College of Ophthalmologists	These are appropriate.	Thank you for your comment. No action required.
	NHS England Specialised Commissioning	More comprehensive glucocorticoid adverse events should be considered, as outlined and referenced in other parts of this response. The OMERACT group have issued guidance on this. It is also important to consider the healthcare costs associated with development of adverse events and glucocorticoid toxicity monitoring, which necessitate frequent attendances within primary and secondary care, see NICE CKS. Cumulative steroid dose and amongst steroids AE – and include infections including severe infections, cataract Also, suggest outcomes also related to the risks of Upadacitinib (in addition to risk of steroids) – e.g. Rates of serious infections, malignancies, and cardiovascular events Due to the age group detailed evaluation of thromboembolic complications needs to be evaluated which are increased in people taking high-dose glucocorticoids, with active aortitis and in people using JAKi. Ensure that the outcomes capture the full range of steroid-related toxicities and costs (e.g osteoporosis, hypertension, type 2 diabetes and associated medications, cardiovascular events, fractures, cataracts,	Thank you for your comment. The scope has been updated with suggested outcomes. Although it is anticipated that adverse effects of long term corticosteroid use will capture health outcomes across the dose range of corticosteroids included in the model, cumulative dose of corticosteroids has been added as a separate outcome to specifically assess the extent to which

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		mood disturbances – and all the medications, clinical appointments and procedures associated with these conditions). Patients where steroids are contraindicated or should be used with extreme caution should also be considered, e.g., those with steroid-related psychosis, or acute myasthenia gravis. The morbidities listed are permanent damage outcomes only. Ensure morbidity from active or chronic disease is captured, including headache, PMR related musculoskeletal pain, joint and muscle stiffness, fatigue, sleep disturbance, weight loss, depression and anxiety.	upadacitinib is corticosteroid sparing
Equality	AbbVie	Limited treatment options exist for GCA which is a disease affecting a majority patient group with protected characteristics: 1. Age: Age is a protected characteristic as per the equality act 2010. GCA is a disease that commonly affects elderly patients, with the average age of onset of disease being 72 years. 2. Disability: Impairments that impact patient's ability to carry out day-to-day functioning are a protected characteristic as per the equality act 2010. GCA is a chronic condition, and several GCA related complications (vision loss) and long-term adverse events associated with corticosteroids (osteoporosis/fracture) can lead to long term impairment for patients. We expect the impact of inequalities to be considered by NICE in their decision-making process.	Thanks for your comments and for outlining potential equalities issue. Equalities issues are not normally listed in the scope. All issues raised are captured in the Equalities Impact Assessment (EIA) form, which will be published alongside the final scope. Where appropriate and relevant, equality issues will be considered by the

Section	Consultee/ Commentator	Comments [sic]	Action
			committee during the evaluation.
	British Society of Rheumatology	Yes, if it followed the model for tocilizumab and was only available after approval from a regional committee located in a specialised “vasculitis” centre, this would be likely to make it more difficult for patients who are under the care of Trusts more distant from the location of the specialised centres. Note the inequities of prescription of tocilizumab in different hospitals within England. Implementation via specialised centre approval (the current model for tocilizumab commissioning for GCA) might 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. More generally, doctors should not be advised to prescribe steroids to older people for lengthy periods because of the well-established side effects. It is also not good to treat older people for 12 months and then offer them nothing else. This would not happen with any other patient group. Allowing the use of Tocilizumab for 12 months alone is a travesty which should not be replicated with Upadacitinib. **Ref** Quick V, Abusalameh M, Ahmed S, Alkoky H, Bukhari M, Carter S, Coath FL, Davidson B, Doddamani P, Dubey S, Ducker G, Griffiths B, Gullick N, Heaney J, Holloway A, Htut EEP, Hughes M, Irvine H, Kinder A, Kurshid A, Lim J, Ludwig DR, Malik M, Mercer L, Mulhearn B, Nair JR,	Thank you for your comment. Comment noted. The committee will consider any relevant equality issues during the evaluation.

Section	Consultee/ Commentator	Comments [sic]	Action
		Patel R, Robson J, Saha P, Tansley S; TOC STOP 2022 Investigators; Mackie SL. 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.]	
	Royal College of Ophthalmologists	This scope is equitable for the disease in the context population.	Thank you for your comment. No action required.
	NHS England Specialised Commissioning	There are substantial inequities in the management of GCA, where older patients are treated with long-term high-dose glucocorticoids, which is no longer acceptable for autoimmune and inflammatory diseases that affect younger people. Restriction of high-cost drugs for GCA also introduces inequities compared with other inflammatory diseases. For example, patients with rheumatoid arthritis and systemic juvenile idiopathic arthritis have the option of continuing treatment until they and their clinicians consider it appropriate to stop (TA247, TA238). This is also consistent with recommended guidance in Takayasu Arteritis, another large vessel vasculitis, which doesn't preclude further courses of Tocilizumab following disease relapse (CCP 16056/P). Upadacitinib is licenced for many autoimmune and inflammatory diseases and most rheumatologists, including at district general hospitals, are familiar with using these drugs. There is thus no need for	Thanks for your comments and for outlining potential equalities issue. Equalities issues are not normally listed in the scope. All issues raised are captured in the Equalities Impact Assessment (EIA) form, which will be published alongside the final scope. Where appropriate and relevant, equality issues will be considered by the

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		older patients to be seen in a specialist centre. MDT approval may be required where there is diagnostic doubt, or where a second opinion is requested. Use of upadacitinib in GCA would improve equity of access to second-line treatment in this group, since it is an oral medication and does not require giving of infusions or subcutaneous injection, which many older people struggle with. It would also provide a second-line treatment option for patients for whom tocilizumab is contraindicated, e.g. those with diverticulitis (which is common in the older age-group). Use of Upadacitinib in GCA would improve equity of access to second-line treatment in this group, since it is an oral medication and does not require giving of infusions or subcutaneous injection. It would also provide a second-line treatment option for patients for whom tocilizumab is contraindicated (e.g. those with diverticulitis which is common in the older age-group), poorly tolerated or ineffective. It would also provide a second line agent in those who relapse after completion of 12 months of tocilizumab. Restricting upadacitinib to one year of use will lead to inequality of care after upadacitinib cessation, as we have seen with tocilizumab in England, given the relapsing nature of GCA. A survey of 29 NHS Rheumatology Centres across England in April 2024 showed that in 14 centres, a total of 30 GCA patients had received a further course of locally-funded tocilizumab to treat a relapse following discontinuation of their NHS England-funded treatment course; whereas in 13 out of the remaining 15 centres treatment was not supported despite GCA patients having met the same NHS England defined relapse	committee during the evaluation.

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		criteria. This demonstrates there is inequality of treatment provision for this population of GCA patients across England. This data can be shared if requested. Therefore, if a choice is made to restrict upadacitinib use to a certain time frame and to continue to limit tocilizumab use to 12 months, then retreatment should be allowed in the event of relapse, as these relapsing patients will have returned to the same disease state they were in when they first started their biologic. The current model for tocilizumab requires approval by a specialist vasculitis centre or approved Bluteq centre for GCA, which makes it more challenging for patients from non-specialist centres to receive treatment for their patients, who may be required to travel to the specialist centre for approval to be given, which discriminates particularly against this older more frail patients with disabilities.	
Other considerations	AbbVie	No comments	Thank you for your comment. No action required.
	British Society of Rheumatology	Why is NICE considering only Upadacitinib and not concurrently reviewing the appropriateness of the current tocilizumab guidance TA518, that tocilizumab therapy can't be given if a patient has already had 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.	Thank you for your comment. Comment noted. TA 518 recommends tocilizumab for use in the NHS. The evaluation will consider current clinical management of GCA without Upadacitinib.

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			Reconsideration of the recommendations for tocilizumab are outside of the remit for this appraisal.
	Royal College of Ophthalmologists	None, see below.	No action required.
	NHS England Specialised Commissioning	Please consider a MTA of UPA and extended use Tocilizumab, so that the non-sensical option of tocilizumab for 12 months, then UPA (even if the tocilizumab was tolerated and effective) does not inevitably occur.	Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme. Reconsideration of the recommendations for tocilizumab are outside of the remit for this appraisal.
Questions for consultation	AbbVie	Where do you consider upadacitinib will fit into the existing care pathway giant cell arteritis? AbbVie expects upadacitinib to be a beneficial treatment option for all patients with giant cell arteritis, including new onset and relapsed patients. Please select from the following, will upadacitinib be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care	Thank you for your comment. No action required

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		C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): Upadacitinib will be prescribed in secondary care with routine follow up in secondary care. For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. Would upadacitinib be used alongside a tapering course of corticosteroids? The setting for prescribing and routine follow up is expected to be the same. Upadacitinib will initially be used alongside a tapering course of corticosteroids (26 weeks), however the SELECT-GCA trial will explore the continued sustained remission after the steroid taper is complete. Would upadacitinib be used in newly diagnosed and/or relapsed or refractory giant cell arteritis? Upadacitinib is anticipated to be used in both newly diagnosed and relapsed GCA. Do you consider that the use of upadacitinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Current biologic treatments for GCA (tocilizumab) require subcutaneous injections, which may be inconvenient and burdensome for some patients and their carers. Upadacitinib is an oral treatment, which could improve adherence and as such there could be broader improvements to a	

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		patients health related quality of life. Substantial improvements in outcomes for people living with GCA may also positively influence the health-related quality of life of their carers or next-of-kin.	
	British Society of Rheumatology	Upadacitinib would be prescribed in secondary care with routine follow-up in secondary care. It would usually be used alongside corticosteroid therapy. It would be likely to be used in relapsed/refractory GCA. Potential guidance on the sequencing of the drugs available – specifically methotrexate, tocilizumab and upadacitinib – would also be helpful, but again taking into consideration the adverse side effects of long-term glucocorticoid treatment which may ultimately result in additional costs to health services.	Thank you for your comments. No action required.

	Royal College of Ophthalmologists	Where do you consider upadacitinib will fit into the existing care pathway giant cell arteritis? 1. **In those people with a positive diagnosis of GCA (US or TAB) and who relapse on glucocorticoids** 2. **In those people with a positive diagnosis of GCA (US or TAB) and who are refractory to glucocorticoids** 3. **In those people with a positive diagnosis of GCA (US or TAB) and who have significant side effects using high dose glucocorticoids (e.g. psychosis or uncontrolled diabetes/hypertension)** Please select from the following, will upadacitinib be: **C. Prescribed in secondary care with routine follow-up in secondary care** For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. **No it should not. GCA is a condition that should be managed in secondary care.** Would upadacitinib be used alongside a tapering course of corticosteroids? **Yes** Would updadacitinib be used in newly diagnosed and/or relapsed or refractory giant cell arteritis? **Yes (see 1-3 above)** Do you consider that the use of upadacitinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? **Yes. Due to the low costs of glucocorticoids the QALY calculation often does not capture the long-term but high burden of side effects**	Thank you for your comments. No action required.

		of glucocorticoids such as loss of bone mass, diabetes and hypertension. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Results from **A Study to Evaluate the Safety and Efficacy of Upadacitinib in Participants With Giant Cell Arteritis (SELECT-GCA)** **ClinicalTrials.gov ID** NCT03725202 Supported by Loricera J, Tofade T, Prieto-Peña D, Romero-Yuste S, de Miguel E, Riveros-Frutos A, Ferraz-Amaro I, Labrador E, Maiz O, Becerra E, Narváez J, Galíndez-Agirregoikoa E, González-Fernández I, Urruticoechea-Arana A, Ramos-Calvo Á, López-Gutiérrez F, Castañeda S, Unizony S, Blanco R. Effectiveness of janus kinase inhibitors in relapsing giant cell arteritis in real-world clinical practice and review of the literature. Arthritis Res Ther. 2024 Jun 5;26(1):116. doi: 10.1186/s13075-024-03314-9 Eriksson P, Skoglund O, Hemgren C, Sjöwall C. Clinical experience and safety of Janus kinase inhibitors in giant cell arteritis: a retrospective case series from Sweden. Front Immunol. 2023 May 25;14:1187584. doi: 10.3389/fimmu.2023.1187584 Sanada A, Abe N, Bohgaki M, Kasahara H. Therapeutic effectiveness of upadacitinib combined with glucocorticoid on remission induction and maintenance in giant cell arteritis. Rheumatology (Oxford). 2022 Aug 30;61(9):e274-e276. doi: 10.1093/rheumatology/keac203	

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	NHS England Specialised Commissioning	*Where will UPA fit into the existing care pathway?* In GCA patients with active disease as indicated above As an alternative treatment to tocilizumab as described above In relapsing or refractory disease: - As an alternative to Tocilizumab (where Tocilizumab is contraindicated, ineffective or more expensive) - As a sequel to 52 weeks treatment with Tocilizumab in the ~50% of patient who relapse (if Tocilizumab was well tolerated and effective then repeat treatment with tocilizumab should be an option here) *Select (ABCD) where UPA will be prescribed:* **C** *For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. Would upadacitinib be used alongside a tapering course of corticosteroids?* Upadacitinib would be used alongside a tapering course of steroids but would NOT be used alongside Tocilizumab. Please note if used in new cranial GCA presentations there are limited data on using shorter durations of glucocorticoids than 6 months, when there is an increased risk of visual loss and care must be taken to deliver safe guidance in this therapeutic window. This may be less critical for pure large vessel GCA or for relapsing disease. Unlike tocilizumab, upadacitinib is an oral medication and there would be reduced resource utilization compared with tocilizumab (no infusion unit, injection training required)	Thank you for your comments. No action required.

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		Would updadacitinib be used in newly diagnosed and/or relapsed or refractory giant cell arteritis? Both *Do you consider that the use of upadacitinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?* It is essential QALY calculations fully consider the costs of glucocorticoid toxicity and impact on quality of life in this age group. A hip fracture or stroke in an older patient may lead to the need for residential care. New data are available, based on CPRD that quantify the dose and time-variant toxicities associated with glucocorticoids. Also, the impact on major cardiovascular events (associated with upadacitinib) and particularly relevant in the demographic affected by GCA. *Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.* SELECT-GCA (double-blind, randomized, PBO-controlled phase 3 clinical trial in 24 countries) assessing upadacitinib vs placebo in 428 patients with GCA EULAR abstract ACR abstract The Leeds group have calculated health care utilisation costs and QALYs associated with major glucocorticoid toxicities and our modelling has been reviewed and verified by colleagues within NICE. This team would be happy to share their models (manuscript submitted to BMJ).	

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		Blockmans et al 2024 (Abstract) https://doi.org/10.1136/annrheumdis-2024-eular.LBA25	
Additional comments on the draft scope	AbbVie	NA	No action required.
	British Society of Rheumatology	• NAIs this expected to be a 12m treatment option like tocilizumab or ongoing? That needs to be made clear. • Will NICE potentially also consider use of Upadacitinib in patients who have previously received a tocilizumab 12m course	Thank you for your comments. The committee will consider the use of upadacitinib based on the evidence presented to it. People who have had up to 12 months of tocilizumab has been added as a potential subgroup in the scope.
	Royal College of Ophthalmologists	No further comments.	No action required.
	NHS England Specialised Commissioning	Consideration of healthcare costs related to corticosteroid-related side-effect in this over 60 year age-group. The 52- week follow-up period of SELECT-GCA study will not be adequate to capture the extent of corticosteroid-related toxicity in this patient group. For example cataracts, fractures and cardiovascular events caused by corticosteroid exposure will often be diagnosed later than 52 weeks after onset of GCA. Costs of corticosteroid-related toxicity have been estimated to be ~£760 per year in patients with asthma [Barry et al 2017 10.1186/s12931-017-0614-x]. This is a much younger population than the group affected by	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		GCA and therefore the health economic costs are likely to be much higher in the GCA group	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Vasculitis UK