National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Tofacitinib for treating active ankylosing spondylitis [ID3865]

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	Novartis	We consider the proposed wording appropriate.	Comment noted. No action required.
	Pfizer	Yes, Pfizer agree that this is an appropriate topic to be referred to NICE.	Comment noted. No action required.
	British Society for Rheumatology (BSR)	Yes, it will be timely and appropriate. This is for the use of Tofacitinib after failure of 2 or intolerance to NSAIDs in Ankylosing Spondylitis	Comment noted. No action required
Wording	Novartis	We consider the proposed appraisal appropriate.	Comment noted. No action required.
	Pfizer	Yes. The wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology that NICE should consider.	Comment noted. No action required.

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	BSR	Yes, it does.	Comment noted. No action required
Timing Issues	Novartis	No comment.	Comment noted. No action required.
	Pfizer	Tofacitinib will provide an alternative class of therapy in addition to nonsteroidal anti-inflammatory drugs (NSAIDs), TNF-alpha inhibitors (TNFi) and IL-17A inhibitors for the treatment of ankylosing spondylitis. Tofacitinib will also provide an oral alternative to the currently available subcutaneous and intravenously administered biologics.	Comment noted. No action required.
	BSR	To be completed in 2021	NICE aims to provide a draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Novartis	The third sentence in the fourth paragraph should be amended to refer to both TA383 and TA497, rather than only TA383.	Comment noted. No action needed. TA497 is for the indication of non-radiographic axial spondylarthritis only. Only some people with non-radiographic axial spondylarthritis will develop ankylosing spondylitis. Because the market authorisation for tofacitinib is limited to only active ankylosing spondylitis, TA497 has been excluded here.
	Pfizer	No comment	Comments noted. No action required.
	BSR	This is accurate and is for radiographic Axial Spa (Ankylosing Spondylitis)	Comment noted. No action required.
The technology/ intervention	Novartis	No comment.	Comment noted. No action required.
	Pfizer	Pfizer request that the wording reflect that tofacitinib has been studied in a clinical trial compared with placebo in the following population	Comment noted. The population description in the PICO table has been amended to

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		Adults with active ankylosing spondylitis who have had an inadequate response or who are intolerant to NSAIDs, and were either biological DMARD (bDMARD) naïve, TNFi-IR (inadequate responder), or bDMARD (non-IR) exposed[(1)] References (1) https://clinicaltrials.gov/ct2/show/NCT03502616 Last accessed 08.02.2021	"People with active ankylosing spondylitis whose disease had responded inadequately to or who are intolerant to non-steroidal anti-inflammatory drugs**".**
	BSR	It should be stated that Tofacitinib is a selective JAK-1 and JAK-3 inhibitor	Comment noted. The background section has now been updated.
Population	Novartis	There is an inconsistency across both the upadacitinib and tofacitinib draft scopes in terms of wording of the population; "active ankylosing spondylitis in adults who have responded inadequately to conventional therapy" is the same as "people with radiographic ankylosing spondylitis for whom nonsteroidal anti-inflammatory drugs have been inadequately effective or not tolerated".	Comment noted. The population description in the PICO table has been amended to "People with active ankylosing spondylitis whose disease had responded inadequately to or who are intolerant to non-steroidal anti-inflammatory drugs"
	Pfizer	Pfizer believe that the population wording should reflect the fact that standard therapy for ankylosing spondylitis is now both NSAIDs and biologics as described in NICE pathway for managing spondyloarthritis in adults [(1)] and NICE guidance [(2,3).]	Comment noted. The population description in the PICO table has been amended to

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		Pfizer request that the population wording be changed to include biologics as described below: “People with active ankylosing spondylitis for whom nonsteroidal anti-inflammatory drugs, or biologics have been inadequately effective or not tolerated” This population would be consistent with the tofacitinib ankylosing spondylitis study A3921120(4), a phase 3, randomised, double blinded, placebo-controlled trial in the following population: Adults with active ankylosing spondylitis who have had an inadequate response or who are intolerant to NSAIDs, and were either bDMARD naïve, TNFi-IR (inadequate responder), or bDMARD (non-IR) exposed. <u>References</u> (1) Managing spondyloarthritis in adults - NICE Pathways. Last accessed 08.02.2021 (2) Overview | TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis | Guidance | NICE. Last accessed 8.02.2021 (3) Overview | Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors | Guidance | NICE. Last accessed 08.02.2021 (4) https://clinicaltrials.gov/ct2/show/NCT03502616 Last accessed 08.02.2021	“People with active ankylosing spondylitis whose disease had responded inadequately to or who are intolerant to non-steroidal anti-inflammatory drugs”
	BSR	Yes, this is for patients who have failed 2 or have intolerance to NSAIDs and have active ankylosing spondylitis.	Comment noted. No action required.

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Comparators	Novartis	The comparator section states 'TNF-alpha inhibitors including:' with secukinumab listed. It should be clear that secukinumab is not a TNF –alpha inhibitor, secukinumab is a human monoclonal antibody which specifically inhibits the interleukin 17A (IL-17A) receptor.	Comment noted. The scope has been amended and the comparator list is now defined as "TNF-alpha inhibitors and interleukin-17A receptor"
	Pfizer	The list of biologic treatments is reflective of those available in the NHS in patients for whom nonsteroidal anti-inflammatory drugs, have been inadequately effective or not tolerated. However given the recommendations in TA383 [(1)], TA407[(2)] and the NICE pathway for Managing spondyloarthritis in adults[(3)] we request that established clinical management without biologics is removed as TNF alpha inhibitors and Secukinumab are recommended as alternatives for patients whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors, Specifically: These guidelines and pathways recommend • Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs [(1)] • Treatment with another tumour necrosis factor (TNF) -alpha inhibitor is recommended for people who cannot tolerate, or whose disease	Comment noted. No action required.

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		has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response [1]. • Secukinumab is recommended, within its marketing authorisation, as an option for treating active ankylosing spondylitis in adults whose disease has responded inadequately to conventional therapy (NSAIDs or TNF-alpha inhibitors)[2] Established clinical management without biologics is therefore not a clinically relevant comparator for patients whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors. References (1) Overview | TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis | Guidance | NICE. Last accessed 8.02.2021 (2) Overview | Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors | Guidance | NICE. Last accessed 08.02.2021 (3) Managing spondyloarthritis in adults - NICE Pathways. Last accessed 08.02.2021	
	BSR	This should include Ixekizumab	Thank you for your comment. Ixekizumab has been included as a comparator in the final scope.

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Outcomes	Novartis	The outcome 'Pain' should be included. 'Pain' as an outcome was included in the scope for TA407, TA383, TA497 and in the scopes for the ongoing appraisals ID1419, 3848 and ID1532.	Pain has been added in the list of outcomes
	Pfizer	The list of outcomes is appropriate.	Comments noted. No action required.
	BSR	The AS Disease Activity Score (ASDAS) should be included	
Economic analysis	Novartis	We consider that it would be more appropriate to move the statement on biosimilars; "The availability and cost of biosimilar products should be taken into account", which is currently included as an "other consideration", to the "economic analysis" section.	Comment noted. No change was made to the template of the scope.
	Pfizer	[redacted]	Comment noted. No action required.
	BSR	The long-term data over 5 years should be considered and comparison against biosimilars	
Equality and Diversity	Novartis	No comment.	Comment noted. No action required.
	Pfizer	No comment. We do not anticipate the recommendation of tofacitinib would lead to any equality concerns	Comments noted. No action required.
	BSR	No further comments	

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Innovation	Novartis	No comment.	Comments noted. No action required.
	Pfizer	Tofacitinib will provide an alternative class of therapy in addition to NSAIDs, TNF-alpha inhibitors and IL-17A inhibitors in the treatment of ankylosing spondylitis. It will also provide an oral alternative to the currently available subcutaneous and intravenously administered biologics.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
	BSR	This is step change and a first in its class as an oral small molecule inhibitor (JAK-1, JAK-3 inhibitor) which will provide an additional option in the treatment of ankylosing spondylitis.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
Other considerations	Novartis	We consider that it would be more appropriate to move the statement on biosimilars; “The availability and cost of biosimilar products should be taken into account”, which is currently included as an “other consideration”, to the “economic analysis” section.	Comment noted. No change was made to the template of the scope
	Pfizer	No comment.	Comment noted. No action required.
	BSR	Cost-effectiveness comparison against biosimilars should be considered	
Questions for consultation	Novartis	In response to the question ‘Where do you consider tofacitinib will fit into the existing NICE pathway, ‘Managing spondyloarthritis in adults’? ‘	Comments noted. No action required.

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		We consider tofacitinib would be positioned as an option alongside biologics.	
	Pfizer	1) Have all relevant comparators for tofacitinib been included in the scope?: **Yes** 2) Which treatments are considered to be established clinical practice in the; NHS for active ankylosing spondylitis?: **NSAIDs, TNF-alpha inhibitors and IL-17 inhibitors** 3) Are the outcomes listed appropriate? **Yes, all outcomes listed are appropriate to include. However, we would note the findings reported in the assessment report of TA383[(1)] that disease progression, i.e. radiographic changes and progression take many years to appear and therefore the evidence from relatively short-term studies must be interpreted with caution** 4) Are the subgroups suggested in 'other considerations appropriate? – **No** 5) Are there any other subgroups of people in whom tofacitinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? **No** 6) Where do you consider tofacitinib will fit into the existing NICE pathway? **Tofacitinib will provide a treatment option for people with active ankylosing spondylitis for whom nonsteroidal anti-inflammatory**	Comment noted. No action required.

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		drugs, or biologics have been inadequately effective or not tolerated **7)** To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. **No. Tofacitinib is already available in the UK for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis** [redacted]NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process: [redacted] **9)** Would it be appropriate to use the cost comparison methodology for this topic?: Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? [redacted] 10) Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?	

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		NCT03502616: Tofacitinib for the treatment of ankylosing spondylitis, a phase 3, randomised, double-blind, placebo-controlled study. In the double-blind phase (weeks 0-16), patients were randomised 1:1 to receive tofacitinib 5 mg BID or placebo. In the open-label phase (weeks 16-48), all patients received open-label tofacitinib 5 mg BID. • **The primary and key secondary endpoints were assessment of spondyloarthritis international Society ≥20% improvement (ASAS20) and ≥40% improvement (ASAS40) responses, respectively, at week 16.** • **Secondary efficacy endpoints analysed at week 16 included: ASAS20/40 response rates stratified by bDMARD treatment history; and change from baseline (Δ) in high sensitivity C-reactive protein (hsCRP), AS Quality of Life (ASQoL) and Short Form-36 Health Survey Version 2 Physical Component Summary (SF-36v2 PCS) score.** • **Secondary efficacy endpoints analysed at week 16 and over time up to week 48 included: ΔAS Disease Activity Score (ASDAS) using hsCRP, ΔBath AS Metrology Index (BASMI)-linear method, ΔFunctional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) total score, ΔASAS components, ASAS partial remission (scores ≤2 for each of the four ASAS components), ASAS 5/6 response (≥20% improvement in ≥5 of 6 components: the four ASAS components, plus hsCRP and spinal mobility [lateral spinal flexion from the BASMI]), ASDAS clinically important improvement (decrease from baseline of**	

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		≥1.1 in patients with baseline scores ≥1.736), ASDAS major improvement (decrease from baseline of ≥2.0 in patients with baseline scores ≥2.636), ASDAS inactive disease (scores <1.3 in patients with baseline scores ≥1.3), ΔBASDAI, BASDAI50 response (≥50% improvement from baseline score), ΔMaastricht AS Enthesitis Score (MASES) in patients with baseline scores >0 and Δswollen joint count in 44 joints (SJC[44]) in patients with baseline counts >0. ASAS20/40 responses were also analysed over time through to week 48. • **Safety was monitored throughout the study, including adverse events (AEs), AEs of special interest (AESI), clinical laboratory abnormalities and laboratory values over time**. **Pfizer considers these outcomes to be clinically relevant** 11) Is there any substantial new evidence for the comparator technology/ies that has not been considered? **For the comparators listed in the draft scope the following trials have been identified as being completed since TA383 and TA407[(3)]** **Sieper J, Deodhar A, Marzo-Ortega H, et al. Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: results from the MEASURE 2 Study. Ann Rheum Dis. 2017;76(3):571-592.** **Kivitz AJ, Wagner U, Dokoupilova E, et al. Efficacy and safety of secukinumab 150 mg with and without loading regimen in**	

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		ankylosing spondylitis: 104-week results from MEASURE 4 study. Rheumatology and therapy. 2018;5(2):447-462. **van der Heijde D, Cheng-Chung Wei J, Dougados M, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. Lancet. 2018;392(10163):2441-2451.** 12) Are there any important ongoing trials reporting in the next year?- **No** References (1) Overview | TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis | Guidance | NICE. Last accessed 8.02.2021 (2) https://clinicaltrials.gov/ct2/show/NCT03502616 Last accessed 08.02.2021 (3) Overview | Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors | Guidance | NICE 08.02.2021	

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

Amgen