National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Sarilumab for previously treated moderate to severe active rheumatoid arthritis

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Sanofi	Yes. We believe it is appropriate for NICE to appraise sarilumab given the complexity of treatment guidance for rheumatoid arthritis. Furthermore we believe sarilumab may be an appropriate technology for evaluation under the new ATA process.	Comment noted. NICE will consider all comments received during the consultation on the draft scope when discussing the appropriateness and suitability of this technology for the Abbreviated Technology Appraisal (ATA) process. No changes to the scope required
Wording	Sanofi	The draft remit wording is appropriate.	Comment noted. No action required.
Timing Issues	Sanofi	None. Marketing authorisation is expected at the [redacted].	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Sanofi	We believe the prevalence figures (based on Symmons 2002) may be out of date. More recent data from the NAO (2009) state rheumatoid arthritis prevalence in England is 580,000.	Commented noted. The prevalence data based on Symmons 2002 is consistent with previous scopes for NICE appraisals in rheumatoid arthritis. No action required.
The technology/ intervention	Sanofi	*Paragraph 1:* The brand name submitted to the EMA is KEVZARA® *Paragraph 2:* A more accurate description of the sarilumab clinical programme is as follows. *"Sarilumab has been studied in randomised controlled trials in combination with conventional DMARDs compared with conventional DMARDs alone in adults with prior conventional DMARD therapy or inadequate response to TNF antagonists, and in monotherapy compared with adalimumab monotherapy in adults who were intolerant to or inappropriate for methotrexate therapy."*	Comment noted. The scope has been amended accordingly.
Population	Roche	It is unclear whether TNF-IR RA patients are the appropriate population for the sarilumab appraisal, since the randomised control trial is in combination with methotrexate and compared to methotrexate monotherapy.	Comment noted. A clinical trial, TARGET, includes people with rheumatoid arthritis who had an inadequate response to TNF inhibitors. This trial compares sarilumab plus DMARDs with placebo plus DMARDs.
	Sanofi	The population is defined appropriately (sub populations are defined below in 'Comparators').	Comment noted. No action required.

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Comparators	Merck Sharpe and Dhome	Golimumab was not mentioned as a comparator when rituximab is contraindicated or withdrawn due to adverse events. Golimumab was recommended in TA225 as an option for patients in whom rituximab is contraindicated or withdrawn due to adverse events and therefore should be included as a comparator in this patient group.	Comment noted. The list of comparators have been amended accordingly.
	Napp Pharmaceuticals	Napp agree with infliximab being listed as a relevant comparator for sarilumab in the following clinical settings: • For moderate or severe active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs. • When rituximab is contraindicated or withdrawn due to adverse events.	Comment noted. No action required.
		Napp support the principal outlined by NICE that "the availability and cost of biosimilar products should be taken into account" when conducting the economic analysis for Sarilumab and would like to reiterate the availability of our biosimilar infliximab Remsima® as a relevant comparator for this appraisal.	Comment noted. No action required.
		Napp also note that rituximab is listed as a relevant comparator in the following setting: • For severe active rheumatoid arthritis that has not responded adequately to therapy with DMARDs including at least one TNF inhibitor. Napp agree with rituximab being listed as a relevant comparator in this setting.	Comment noted. No action required.
		[redacted]	Comment noted. No action required.

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	Roche	Sarilumab comparators listed in the draft scope include TNF inhibitors and biologics although there seems to be no clinical trial to support an appraisal for this stage in the treatment pathway.	Comment noted. One of the clinical trials, TARGET, includes people with rheumatoid arthritis who had an inadequate response to TNF inhibitors.
		If the ongoing certolizumab pegol NICE appraisal does not recommend treatment for severe active RA that has not responded adequately to therapy with DMARDs including at least one TNF inhibitor, then certolizumab pegol should be removed as a comparator in this patent group.	Comment noted. The comparators in the scope have been up-dated to take account of the recommendations in the NICE technology appraisal 415 'Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor'.

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	Sanofi	Under the ATA process, we believe the most appropriate comparators are tocilizumab and adalimumab. Tocilizumab is currently the only NICE recommended biological DMARD for rheumatoid arthritis affecting the same physiological pathway as sarilumab (the IL-6 pathway), and both tocilizumab and adalimumab were investigated with sarilumab in the late phase study programme. In ASCERTAIN, which investigated the safety and tolerability of sarilumab SC compared to tocilizumab IV in combination with conventional DMARDs, no clinically meaningful difference in clinical adverse events was found between treatment groups. In MONARCH, which investigated the efficacy of sarilumab SC compared to adalimumab SC in monotherapy, sarilumab demonstrated superiority in improving signs, symptoms and physical function. If the appraisal follows the STA process, we believe the first population *"For moderate or severe active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs"* and associated comparators are not in line with current NICE guidance. We suggest this population is divided for consistency as follows: • For moderate active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs: o Best supportive care • For severe active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs: o Biological DMARDs in combination with methotrexate (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept) o Adalimumab, etanercept, certolizumab pegol, or tocilizumab (each as monotherapy) We believe the other populations stipulated *"For severe active rheumatoid arthritis that has not responded adequately to therapy with DMARDs including at least one TNF inhibitor"*, *"When rituximab is contraindicated or withdrawn due to adverse events"* and *"For people with moderate to severe, active disease despite treatment with biological DMARDs recommended according to NICE guidance"* along with the respective stated comparators are appropriate	Comment noted. NICE will consider the appropriateness for an ATA process, once the methods and processes for ATA are finalised. Comment noted. The comparators in the scope have been up-dated accordingly.

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Outcomes	Abbvie	All outcomes defined in the scope are fine except for extra-articular manifestations of the disease which should be removed since extra-articular manifestations are primarily associated with spondyloarthritides.	Comment noted. The inclusion of extra-articular manifestation as an outcome is consistent with previous scopes for NICE appraisals in rheumatoid arthritis. No action required.
	Sanofi	The outcomes of interest are appropriate.	Comment noted. No action required.
Economic analysis	Abbvie	For comparison with previously conducted technology appraisals it will be important to ensure analyses are conducted using the same assumptions on time horizon and discount rates.	Comment noted. No action required.

	Napp Pharmaceuticals	Napp welcome the proposed consideration within the draft scope that "The availability and cost of biosimilar products should be taken into account." Napp would recommend that in order to accurately reflect the true NHS acquisition cost of biosimilar medicines that actual tender prices are included for biosimilar medicines, and not just the list price. If information relating to actual tender prices is not available, Napp would suggest that uncertainty related to acquisition cost could be handled as a sensitivity analysis covering a range of discounts (i.e. 10%, 20%, 30%, 40%, 50%, etc).	Comment noted. No action required. Comment noted. Section 5.5.2 of NICE's guide to the methods of technology appraisal (2013) states '….. When there are nationally available price reductions, for example for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit, then the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS. Analyses based on price reductions for the NHS will only be considered when the reduced prices are transparent and consistently available across the NHS, and if the period for which the specified price is available is guaranteed.' No action required.

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	Sanofi	We believe a cost-comparison analysis alongside a review of the clinical evidence is appropriate if the ATA process is adopted. However, if this topic follows the STA process, we believe the reference case would be suitable.	Comment noted. No action required.
Equality and Diversity	Sanofi	No foreseen equality concerns.	Comment noted. No action required.
Other considerations	Sanofi	As outlined in the 'Comparators' section, we believe a population subgroup of patients with moderate active disease (DAS28 >3.2 <5.1) should be considered separately to be consistent with current guidance if the STA process is adopted. We also believe it may be appropriate to consider subgroups of patients with seropositive or seronegative antibody status. It is not yet clear if appropriate evidence is available to consider the primary/secondary failure following initial TNF inhibitor failure subgroup.	Comment noted. As stated in the scope, if evidence allows, the appraisal will consider the listed subgroups. If evidence does not allow, justifications should be presented to the Committee.
Innovation	Abbvie	Sarilumab is the second IL-6 to be introduced in the UK market, with no discernible additional benefits with efficacy or safety over tocilizumab.	Comment noted. The Appraisal Committee will discuss the potentially innovative nature of this technology. No changes to the scope required.

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	Sanofi	We do not consider sarilumab to be a step-change in the management of rheumatoid arthritis however we do believe it is a significant addition to the currently available treatments. Not all patients respond to every therapy and patients often experience a loss of effectiveness whilst on therapy. It is important therefore that an increased number of treatments are available providing more options for the optimal sequencing of therapy for this long-term chronic disease. We believe there may be workplace and household activity benefits, which are not captured by the QALY, associated with the use of sarilumab due to the debilitating effects of rheumatoid arthritis however only limited productivity data was captured in the sarilumab clinical trial programme.	Comment noted. The Appraisal Committee will discuss the potentially innovative nature of this technology. No changes to the scope required. Any benefits that have not been captured in the estimate of the QALY and which are supported by evidence will be considered by the appraisal committee.
Questions for consultation	Abbvie	*Have all relevant comparators for sarilumab been included in the scope for the 3 populations?* All relevant comparators for sarilumab have been included. *Which treatments are considered to be established clinical practice in the NHS for rheumatoid arthritis after conventional DMARDs or TNF inhibitors?* • Conventional treatments after DMARDS (e.g., TNF inhibitors, Tocilizumab and Abatacept). NFs likely to remain first line as costs are driven down by biosimilar entrants). • Conventional treatments after TNF inhibitors (e.g., 2nd line TNF, tocilizumab, abatacept and rituxumab) *Where do you consider sarilumab will fit into the existing NICE pathway, Rheumatoid arthritis?* Sarilumab might be used in clinical practice as an alternative to tocilizumab.	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

	Sanofi	*Have all relevant comparators for sarilumab been included in the scope for the 3 populations?* We believe all relevant comparators have been included for the populations as defined above in the 'Comparators' section. *Which treatments are considered to be established clinical practice in the NHS for rheumatoid arthritis after conventional DMARDs or TNF inhibitors?* We believe all the comparators outlined above are established clinical practice in the NHS following conventional DMARD therapy or TNF inhibitor therapy. *Are the outcomes listed appropriate?* Yes, we believe so. *Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom sarilumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?* We believe the subgroups detailed in 'Other considerations' are appropriate however it is not clear whether appropriate evidence is available to evaluate the primary/secondary failure following initial TNF inhibitor therapy subgroup. Where do you consider sarilumab will fit into the existing NICE pathway, *Rheumatoid arthritis*? We believe sarilumab fits into the Rheumatoid arthritis treatment pathway after conventional DMARD therapy in combination with methotrexate or monotherapy, and after TNF inhibitor therapy in combination with methotrexate. *NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:*	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

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		- *could have any adverse impact on people with a particular disability or disabilities.* We do not believe the remit and scope adversely affect any equality considerations. - *Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.* None required.	

	Sanofi	*identify and consider such impacts.* None required. *Do you consider sarilumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* We do not consider sarilumab to be a step-change in the management of the disease however we believe it is a significant addition to the currently available therapies. Patients often experience a loss of effectiveness whilst on therapy and some patients may not respond to other treatments. It is important therefore that an increased number of therapies providing more options for the optimal sequencing of treatment are available for this long term chronic disease. *Do you consider that the use of sarilumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* We believe there may be workplace and household activity benefits, which are not captured by the QALY, associated with the use of sarilumab due to the debilitating effects of rheumatoid arthritis. *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* Limited productivity data was captured in the sarilumab clinical trial programme.	Comment noted. No action required. The Appraisal Committee will discuss the potentially innovative nature of this technology. No changes to the scope required. Any benefits that have not been captured in the estimate of the QALY and which are supported by evidence, will be considered by the appraisal committee. Any benefits that have not been captured in the estimate of the QALY and which are supported by evidence, will be considered by the appraisal committee.

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	Sanofi	NICE intends to appraise this technology through its Technology Appraisal Process. NICE is currently consulting on an additional technology appraisal process; known as the Abbreviated Appraisal Process (ATA). More information on the consultation is available at https://www.nice.org.uk/about/what-we-do/ourprogrammes/nice-guidance/nice-technologyappraisal-guidance/abbreviated-technologyappraisal-process-consultation. We welcome comments on the appropriateness and suitability of considering the new ATA process for appraising this topic. Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction We believe the new ATA process would be appropriate for sarilumab in comparison with tocilizumab and/or adalimumab. We are conscious however that this approach would not address the unmet need for therapies for patients with moderate active disease who have failed on conventional DMARDs. This subgroup of patients falls under (the anticipated) licence and we believe it is important that they are able as sarilumab when clinical benefit. We also recognise the findings from TA375 that there is great uncertainty in the cost-effectiveness of biological DMARDs in this subgroup which precludes access at present. We understand that NICE is further investigating this area to address the unmet need and we fully support them in doing so. present. We understand that NICE is further investigating this area to address the unmet need and we fully support them in doing so.	Comments noted. NICE will consider the appropriateness for an ATA process, once the methods and processes for ATA are finalised. No changes to the scope required.

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

Department of Health
Pfizer