National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Tildrakizumab for treating moderate to severe plaque psoriasis

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	Almirall	Yes, this is an appropriate topic to refer to NICE in order that guidance on the use of tildrakizumab can be issued to the NHS in England and Wales.	Comment noted. No action required.
	Janssen	Janssen believes this is an appropriate topic to refer to NICE for appraisal	Comment noted. No action required.
	Novartis	We consider the proposed appraisal appropriate.	Comment noted. No action required.
	Psoriasis and Psoriatic Arthritis Alliance	It would be appropriate to appraise tildrakizumab	Comment noted. No action required.
Wording	Janssen	The wording of the remit is different compared to previous NICE scopes for plaque psoriasis that stated “To appraise the clinical and cost effectiveness of [molecule name] within its marketing authorisation for treating moderate to severe plaque psoriasis.”	Comment noted. In line with previous NICE scopes for plaque psoriaris, the remit has

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		Tildrakizumab remit included the sentence “who are candidates for systemic therapy”, however it is not clear if it refers to conventional systemic therapies, to biologics systemic therapies or both.	been amended to: ‘To appraise the clinical and cost effectiveness of tildrakizumab within its marketing authorisation for treating moderate to severe plaque psoriasis’.
	Novartis	There is no clear definition of “moderate to severe plaque psoriasis”. Our understanding is that the Phase III studies of tildrakizumab in plaque psoriasis recruited patients with psoriasis area and-severity index (PASI) score of 12 or higher, Investigator’s Global Assessment [IGA] score of 3 or higher and involvement of 10% or more of the body-surface area.1 The population for whom evidence on tildrakizumab clinical efficacy is available is therefore closely aligned to the populations included in studies of secukinumab and other biologic agents.2-5 Whilst secukinumab and other biologic agents have marketing authorisation for treatment of moderate to severe plaque psoriasis,6-11 NICE recommendations for these products refer to severe disease.12-16 We therefore suggest that the appraisal should focus on patients with severe psoriasis.	Comment noted. The remit reflects the expected marketing authorisation of tildrakizumab. In line with previous NICE scopes for plaque psoriaris, the remit has been amended to: ‘To appraise the clinical and cost effectiveness of tildrakizumab within its marketing authorisation for treating moderate to severe plaque psoriasis’.
	Psoriasis and Psoriatic Arthritis Alliance	Yes, as long as it reflects final licensed indication	Comment noted. In line with previous NICE scopes for plaque psoriaris, the remit has been amended to: ‘To

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			appraise the clinical and cost effectiveness of tildrakizumab within its marketing authorisation for treating moderate to severe plaque psoriasis'.
Timing Issues	Almirall	In order to ensure the NHS is provided with timely guidance on the use of tildrakizumab the appraisal should be scheduled to ensure this is issued as close as possible to marketing authorisation.	Comment noted. NICE aims to issue draft or final guidance to the NHS within 6 months of the product being first licensed in the UK (for non-cancer drugs). No action required.
	British Association of Dermatologists	Should be assessed as soon as possible – innovative treatment	Comment noted. No action required.
	Janssen	The timing of this appraisal is appropriate	Comment noted. No action required.
	Psoriasis and Psoriatic Arthritis Alliance	No particular urgency, as other similar class therapies are available.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AbbVie	This wording on page 1 that describes the pathway in Clinical Guideline 153 states the following “Systemic non-biological therapies are recommended for people whose psoriasis does not respond to topical therapy and is extensive, associated with significant functional impairment and distress or for people for whom phototherapy has been ineffective or cannot be used to treat their psoriasis.” It should read as follows: “Systemic non-biological therapies are recommended for people whose psoriasis cannot be controlled with topical therapy and is associated with significant impact on physical, psychological or social wellbeing and psoriasis is extensive or localised and associated with significant functional impairment and/or high levels of distress or phototherapy has been ineffective, cannot be used or has resulted in rapid relapse ”	Comment noted. The recommendations on the use of systemic non-biological therapies have been updated in line with NICE clinical guideline 153.
	Almirall	The information provided on published NICE technology appraisals should be updated to include the NICE technology appraisal for ixekizumab (TA442) published in April.	Comment noted. NICE technology appraisal 442 on ixekizumab has been included in the information on published NICE technology appraisal guidance.
	Novartis	Within the fifth paragraph we recommend that “ciclosporin, methotrexate or PUVA” should be changed to “ciclosporin, methotrexate and PUVA” to more closely reflect the wording of guidance.	Comment noted. The background section has been amended to reflect this comment.
	Psoriasis and Psoriatic Arthritis Alliance	Add psoriatic arthritis as an associated condition.	Comment noted. This scope focuses on

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			plaque psoriasis only. No action required.
The technology/ intervention	Almirall	In order to accurately describe tildrakizumab the following underlined additions are proposed: '*Tildrakizumab (brand name unknown, Merck Sharp & Dohme) is a high-affinity anti IL-23p19 monoclonal antibody that selectively blocks the p19 subunit of interleukin-23 which plays a key role in the pathogenesis of psoriasis ~~is thought to inhibit interleukin-23 (IL-23), a receptor which plays an important role in the pathogenesis of autoimmune inflammation~~. Tildrakizumab is administered by subcutaneous injection.'*	Comment noted. The technology section has been updated to reflect this comment.
	Novartis	The draft scope indicates that Merck Sharp & Dohme are the sponsors for the tildrakizumab appraisal. However, the provisional matrix lists the company as Almirall. Our understanding is that although Merck Sharp & Dohme were involved in the development of tildrakizumab, Almirall hold the commercialisation rights in Europe. We suggest that Almirall rather than Merck Sharp & Dohme should be specified under "The Technology".	Comment noted. The company name has been corrected to Almirall.
	Psoriasis and Psoriatic Arthritis Alliance	Appears to match description in trial data.	Comment noted. No action required.
Population	AbbVie	We believe this should read "adults with moderate to severe plaque psoriasis."	Comment noted. The population section has been updated to reflect this comment.
	Almirall	Tildrakizumab will be an alternative treatment in the systemic biological therapy part of the psoriasis treatment pathway as defined in NICE CG153 and the NICE pathway for psoriasis.	Comment noted. The population section has

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		In order to accurately reflect the anticipated licensed indication the population should be defined as follows: '*Adults ~~people~~ with moderate to severe psoriasis who are candidates for systemic therapy'* There are no subgroups within the population which should be considered separately.	been updated to reflect this comment.
	British Association of Dermatologists	The population is appropriate	Comment noted. No action required.
	Janssen	To be consistent with previous appraisals we suggest to use the word "adults" instead of "people"	Comment noted. The population section has been updated to reflect this comment.
	Novartis	We recommend that the wording is changed from "people" to "adults" with moderate to severe plaque psoriasis as we understand that only people aged 18 years or over were recruited into the reSURFACE 1 (NCT01722331) and reSURFACE 2 studies (NCT01729754).17-18 There is no clear definition of "moderate to severe plaque psoriasis". Our understanding is that the Phase III studies of tildrakizumab in plaque psoriasis recruited patients with psoriasis area and-severity index (PASI) score of 12 or higher, Investigator's Global Assessment [IGA] score of 3 or higher and involvement of 10% or more of the body-surface area.1 The population for whom evidence on tildrakizumab clinical efficacy is available is therefore closely aligned to the populations included in studies of secukinumab and other biologic agents.2-5 Whilst secukinumab and other	Comment noted. The population section has been updated from 'people' to 'adults'. However, 'moderate to severe plaque psoriasis' has been retained as it reflects the expected marketing authorisation of tildrakizumab.

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		biologic agents have marketing authorisation for treatment of moderate to severe plaque psoriasis,6-11 NICE recommendations for these products refer to severe disease.12-16 We therefore suggest that the appraisal should focus on patients with severe psoriasis.	
	Psoriasis and Psoriatic Arthritis Alliance	Maybe say adult population >18 years as per trial.	Comment noted. The population section has been updated to reflect this comment.
Comparators	AbbVie	We believe that the comparator scope should be in line with that for guselkumab (except that we do not believe than best supportive care (BSC) is an appropriate comparator for this scope, nor in fact for guselkumab).. The rationale for this is provided below in this comment box. Comparators should therefore be: If non-biologic systemic treatment or phototherapy is suitable: □ Systemic non-biological therapies including acitretin, ciclosporin, fumaric acid esters (including dimethyl fumarate and guselkumab subject to ongoing NICE appraisal) and methotrexate □ Phototherapy with ultraviolet (UVB) radiation For people with severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated: □ TNF-alpha inhibitors (etanercept, infliximab, adalimumab) □ Ustekinumab □ Secukinumab □ Apremilast □ Guselkumab (subject to ongoing NICE appraisal)	Comments noted. Comparators for people who can have non-biologic systemic treatment or phototherapy have been added. Best supportive care has been retained because it is the only treatment option for people unable to take any of the available alternative therapies.

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		We do not believe that best supportive care is an appropriate comparator. Patients who receive tildrakizumab would in the absence of tildrakizumab receive a different treatment rather than receive no treatment (ie. BSC). For this reason it would be appropriate in an incremental analysis to include BSC following failure of a certain number of treatments but it would not be appropriate to compare tildrakizumab in a pairwise analysis versus BSC.	
	Almirall	The listed comparators including best supportive care are appropriate. As stated above tildrakizumab will be an alternative treatment in the systemic biological therapy part of the psoriasis treatment pathway. In line with the other biologics and apremilast, use will be after the systemic non-biological therapies (such as ciclosporin, methotrexate and acitretin) and as a consequence these therapies are not relevant comparators for tildrakizumab.	Comment noted. Comparators for people who can have non-biologic systemic treatment or phototherapy have been added.
	British Association of Dermatologists	Methotrexate and fumaric acid esters (unlicensed but used in the psoriasis population with moderate severity) should be considered in the comparator group?	Comment noted. Comparators for people who can have non-biologic systemic treatment or phototherapy have been added.
	Janssen	The remit indicates that tildrakizumab could potentially be use alongside conventional systemic therapies which are not included as comparators in this draft scope. We would suggest to use the same comparators listed in brodalumab and guselkumab NICE draft scopes: If non-biologic systemic treatment or phototherapy is suitable:	Comment noted. Comparators for people who can have non-biologic systemic treatment or phototherapy have been added.

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		• Systemic non-biological therapies (including acitretin, ciclosporin, fumaric acid esters, methotrexate, tacrolimus) • Phototherapy with ultraviolet (UVB) radiation For people with severe or very severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated: • TNF-alpha inhibitors (etanercept, infliximab, adalimumab) • Ustekinumab • Secukinumab • Apremilast • Ixekizumab • Best supportive care Additionally, brodalumab and/or guselkumab may be relevant comparators to be considered for the final scope if they are license for use in the UK.	Brodalumab and guselkumab have been added as comparators "(subject to ongoing NICE appraisal)".
	Novartis	Since the remit is to consider the cost-effectiveness of tildrakizumab within the full licensed population, the appropriate comparators will differ across subpopulations. Specifically, if non-biologic systemic treatment or phototherapy is suitable then the appropriate comparators are: • Systemic non-biological therapies including methotrexate, ciclosporin and fumaric acid esters • Phototherapy, including with ultraviolet (UVB) radiation or psoralen-ultraviolet A (PUVA)	Comment noted. Comparators for people who can have non-biologic systemic treatment or phototherapy have been added.

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		For patients with very severe psoriasis (as defined by a total PASI score of 20 or more and a DLQI score of more than 18) infliximab should be included as an additional comparator alongside the other biologic therapies.	Infliximab has been added to the list of comparators.
	Psoriasis and Psoriatic Arthritis Alliance	Infliximab is in use for severe group PASI >20 Best supportive care needs to be clearly defined in the appraisal, given where this drug is going to be positioned following inadequate response of other therapies.	Comments noted. Infliximab has been added to the list of comparators.
Outcomes	AbbVie	We believe that in place of this wording " psoriasis symptoms on the face, scalp and nails" a better outcome to include would be "improvements of nails, high impact / difficult to treat sites (including face & scalp) and joint outcomes"	Comment noted. This outcome has been updated to 'psoriasis symptoms on the face, scalp, nails and joints'.
	Almirall	Data on the outcome 'psoriasis symptoms on the face, scalp and nails' is not available for tildrakizumab and on this basis we would propose this outcome is removed from the scope. In order to ensure all health related benefits are captured maintenance of response rate should also be included as a relevant outcome.	Comment noted. The outcomes in the scope reflect the measures of health benefits and adverse effects that are important to patients and/or their carers. The outcome 'duration of response' has been added to the scope.

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	British Association of Dermatologists	Additional outcomes that should be considered includes: • Other high-impact and difficult-to-treat sites: - palms - soles - flexures - genitals • Injection site reactions • Mood, psychological or social functioning	Comment noted. The listed outcomes are captured in the scope under 'psoriasis symptoms on the face, scalp, nails and joints', 'adverse effects of treatment' and 'health-related quality of life'. No action required.
	Novartis	In general the outcomes specified are appropriate. We note that consideration of tildrakizumab's benefits in treating psoriasis symptoms on the face, scalp and nails would require additional studies adequately powered to detect statistically significant differences between interventions on these outcomes. In addition, given the short-term nature of most clinical studies in psoriasis, we consider it unlikely that adequate data to support mortality endpoints will be available.	Comment noted. The outcomes in the scope reflect the measures of health benefits and adverse effects that are important to patients and/or their carers. No action required.
	Psoriasis and Psoriatic Arthritis Alliance	The secondary outcome in the reSURFACE 1 trial of PASI 90 AND PASI 100 (clearance) should be seen as the goal of any newly appraised drug. Minimal disease actvity is potentially acceptable, but only achieving PASI 75 is not that meaningful to patients anymore, as that still can leave visible psoriasis, for some people is not acceptable. Psychological impact is an important factor to measure, along with the effect the condition has on carers and family members, clearing psoriasis improves more than just the patient's outlook.	Comment noted. The listed outcomes are captured in the scope under 'severity of psoriasis' and 'health-related quality of life'. No action required.

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Economic analysis	Almirall	An economic analysis that addresses the requirements of the NICE reference case will be submitted. The anticipated time horizon will be 10 years in line with previous economic analyses for psoriasis however consideration will be given to a longer, 25 year, time horizon.	Comment noted. No action required.
	Psoriasis and Psoriatic Arthritis Alliance	Psoriasis is a relapsing/remitting life-long disease that often starts in teenage years and can last well into old age, so long-term benefit and adverse events needs to be included within the lifetime case.	Comment noted. No action required.
Equality and Diversity	Psoriasis and Psoriatic Arthritis Alliance	None that we are aware.	Comment noted. No action required.
Innovation	Almirall	Not applicable. Tildrakizumab is however innovative with regard to its mode of action and is the first high-affinity anti IL-23p19 monoclonal antibody.	Comment noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.

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	British Association of Dermatologists	Yes – this technology is novel, targeting a distinct pathway, and important to have as an option due to patients' varying responses to other biologic drugs Yes – neither the DLQI (the commonly used tool for impact in skin disease, or the EQ5D) encompass distress or low mood. These are extremely common in people with moderate-to-severe psoriasis and are known to improve with disease control	Comment noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
	Psoriasis and Psoriatic Arthritis Alliance	Yes to a certain degree, given the IL-23 p19 target is different to other similar class, although it could be argued that this is a progression and not a 'step change'.	Comment noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
Other considerations	AbbVie	We believe that the following statement should be removed from the scope because it is inconsistent with the NICE methodological guidance: "To account for potential bias from including non-cost-effective comparators within sequences of treatments, comparisons of each treatment alone against best supportive care could be explored." In the comparator section we state that we do not believe that BSC is an appropriate comparator for pairwise analysis and our rationale for this belief. In addition, it is not appropriate at a scope stage to determine the approach to analysis based upon an assumption that certain treatment comparators may not be cost effective. This is a decision for the Appraisal Committee to establish the most appropriate comparators. As stated in section 2.2.4. of the NICE methods guidance 2013 "The scope identifies all potentially relevant comparators, taking into account issues likely to be considered by the Appraisal Committee when selecting the most appropriate comparator At this stage of the appraisal, identification of comparators should be inclusive."	Comment noted. The statement referred to has been removed from the scope.

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		If the within the scope it is thought desirable to make reference to the decision that may be taken by the Committee in relation to deciding upon appropriate comparators it should be in line with the approach outlined in section 6.2.3. which states the following: The Committee will normally be guided by established practice in the NHS when identifying the appropriate comparator(s). When the assessment suggests that an established practice may not be considered a good use of NHS resources relative to another available treatment, the Committee will decide whether to include it as an appropriate comparator in the appraisal, after reviewing an incremental cost–utility analysis. The Committee's overall decision on whether it is a valid comparator will be guided by whether it is recommended in other extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology. The Committee will also take into account the uncertainty associated with the estimates of clinical and cost effectiveness, and whether the new technology under appraisal could provide a cost-saving alternative. Reference to the exclusion of non-cost effective comparators from analysis should therefore refer to the fact that this decision is under the remit of the Committee not the scope, subject to whether such treatments are covered by extant NICE guidance and / or whether its use is embedded in clinical practice. It is noted that this language has not been included in previous scopes (at least for drugs appraised in psoriasis).	
	Janssen	We suggest to incorporate phototherapy in this subgroup “the previous and systemic non-biological therapy”. With the inclusion, the subgroup would state “previous use of phototherapy and systemic non-biological therapy”.	Comment noted. The subgroups in the scope have been amended to reflect this comment.

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	Psoriasis and Psoriatic Arthritis Alliance	Many other drugs in this class are also used for psoriatic arthritis, which may influence prescribing, if a patient has both conditions. There are trials being conducted in psoriatic arthritis, any potential benefit this drug has for that group could be useful.	Comment noted. This scope focuses on plaque psoriasis only. No action required.
Questions for consultation	Almirall	We agree that an appraisal of tildrakizumab via the Single Technology Appraisal (STA) process is appropriate with an appraisal scheduled to ensure guidance is issued as close as possible to marketing authorization. It is not anticipated that tildrakizumab will be appropriate for consideration using cost comparison methodology and on this basis specific responses to the consultation questions are not provided.	Comment noted. No action required.
	Novartis	Have all relevant comparators for tildrakizumab been included in the scope? *Novartis: See comments above on "comparators". On the basis that best supportive care has been included as a comparator in all previous appraisals of technologies for chronic plaque psoriasis, we consider it appropriate that it is also included amongst the comparators for tildrakizumab.* Are the outcomes listed appropriate? *Novartis: See comments above on "Outcomes".* Are the subgroups suggested in 'other considerations appropriate? *Novartis: Nothing further to add beyond previous comments that moderate and severe psoriasis are poorly defined, and that for adults with very severe psoriasis, infliximab should also be considered a relevant comparator.* Where do you consider tildrakizumab will fit into the existing NICE pathway for psoriasis? *Novartis: Since tildrakizumab is likely to be the ninth biologic available in the UK for chronic plaque psoriasis, we would expect it to be positioned alongside or after the other biologics recommended by NICE.* NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular	Comment noted. Please see above responses to comments on 'population', 'comparators', and 'outcomes'.

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		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. *Novartis: No comment.* Do you consider tildrakizumab 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? *Novartis: No comment.* Do you consider that the use of tildrakizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? *Novartis: No comment.* We welcome comments on the appropriateness and suitability of the cost comparison methodology to this topic. *Novartis: Tildrakizumab may be suitable for cost comparison provided there is evidence to support health benefits that are similar or greater to those of secukinumab and the other biologic therapies, at a similar or lower cost.* Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? *Novartis: No comment.* Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? *Novartis: We note that the primary endpoints of the reSURFACE 1 and reSURFACE 2 studies include PASI 75 whilst PASI 90 and PASI 100 were secondary endpoints.*[17, 18] *PASI 90 is increasingly recognised as the best evidence of efficacy*.[19] Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?	

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		Novartis: The CLEAR study[20] was not available during the appraisal of secukinumab in plaque psoriasis (TA350). In this head-to-head, double-blind study, secukinumab demonstrated sustained superior *efficacy in comparison with ustekinumab in clearing skin through to week 52, greater improvement in quality of life, and a favourable and comparable safety profile.*	
	Psoriasis and Psoriatic Arthritis Alliance	Tildrakizumab probably should be considered at the same point as other biologic agents (third line).	Comment noted. No action required.

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

Celgene
Department of Health and Social Care
Royal College of Physicians endorsed British Association of Dermatologists response