NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tildrakizumab for treating chronic plaque psoriasis after systemic therapy [ID1060]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Almirall
   - Psoriasis and Psoriatic Arthritis Alliance
   - British Association of Dermatologists
     the Royal College of Physicians endorsed this statement
   - Celgene
   - Leo Pharma
   - Novartis

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Appendix of new evidence –** submitted by Almirall

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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 number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Almirall	Almirall appreciate the opportunity to respond to the Appraisal Consultation Document (ACD) for tildrakizumab for treating adults with moderate to severe plaque psoriasis for whom systemic treatment is appropriate. We confirm that all the relevant evidence has been taken into account and the summaries of clinical and cost-effectiveness are reasonable interpretations of that evidence. We are disappointed that the provisional recommendations do not recommend tildrakizumab particularly since the unmet need for additional treatment options in this group of patients is clearly recognised (ACD section 3.2)	Comment noted.
2	Company	Almirall	With the agreement of NICE, we have submitted additional cost-effectiveness estimates (as a separate document) to address the points raised by the Appraisal Committee (ACD Section 3.23). We hope that the additional cost-effectiveness analyses provided will enable the Committee to recommend tildrakizumab as a cost-effective option following the second Appraisal Committee meeting.	The committee considered the additional cost-effectiveness estimates. Please see section 3.24 of the final appraisal document.
3	Patient group	Psoriasis and Psoriatic Arthritis Alliance	Although is it always going to be disappointing to people with psoriasis to see that a new therapy for their disease will not be routinely available as part the treatment pathway, we accept that any new therapy must be cost-effective to the NHS.	Comment noted.
4	Patient group	Psoriasis and Psoriatic Arthritis Alliance	It is unfortunate that the data supplied for tildrakizumab did not provide sufficient evidence to help the committee make a positive recommendation.	Comment noted.
5	Patient group	Psoriasis and Psoriatic Arthritis Alliance	As users of NHS services our constituent group want to have confidence in the therapies offered and as with other chronic conditions, need access to a wide range of therapies as efficacy wanes. Fortunately for psoriasis patients there are a number of similar therapies approved and available. So this decision is less urgent, but we would hope that the manufacturer will endeavour to provide the answers needed to allow the committee to reconsider this initial decision, as any additional choice is welcomed.	Comment noted. Please see section 3.2 of the final appraisal document.
6	Patient group	Psoriasis and Psoriatic Arthritis	We believe as an organisation that as newer therapies become available for appraisal, patients deserve each subsequent therapy to provide substantial	Comment noted.

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		Alliance	improvement on current therapies, if the product provides the same effectiveness, then it does appear reasonable for the NHS to seek a better commercial price, which will not only help those with psoriasis but others who also rely on cost effective treatments within the NHS.	
7	Professional group	British Association of Dermatologists	In relation to the discussion as to whether efficacy of tildrakizumab be assessed at 12 weeks or 28 weeks, in clinical practice it is not possible to keep a patient with severe disease on a drug for 7 months in hope of efficacy which is not materialising. In reality, a decision will be made far earlier than this (e.g. 12 weeks), based perhaps on lesser degrees of response. A model allowing continuation to 28 weeks to assess PASI75 in those who achieve a partial response (e.g. PASI50) earlier may be helpful	The text has been amended to reflect this. Please see sections 1.2 and 3.11 of the final appraisal document.
8	Professional group	British Association of Dermatologists	Experience with TNF and IL17 inhibitors have shown how important it is in practice to have more than one agent in a therapeutic class	Comment noted. Please see section 3.2 of the final appraisal document.
9	Professional group	British Association of Dermatologists	The importance of 3 monthly injections (compared with monthly injections with the other licensed drug in this class) to patients and carers should be considered	Comment noted. Please see section 3.26 of the final appraisal document.
10	Commentator	Celgene Ltd	Celgene does not agree with the conclusions reached in Section 3.5 of the ACD. The following points outline the reasoning for apremilast to be included as a relevant comparator during decision making. • Celgene has on-file market share data, which shows that the use of apremilast is established in NHS clinical practice, deeming it a relevant comparator as in line with the NICE Methods Guide.[1] Apremilast is also recommended by NICE in line with biologic therapies and dimethyl fumarate[2], and its use is expected to continue unless and until it is replaced by a new technology. • Conclusions drawn as to the perceived effectiveness of apremilast are also inaccurate. Apremilast is an established treatment in NHS clinical practice, with clinical advocacy, as well as real-world evidence supporting both its effectiveness and relevance as a comparator in NICE appraisals of technologies for treating moderate to severe plaque psoriasis.[3,4] • Apremilast is also an established treatment option for psoriasis in the British Association of Dermatologists Biologics and Immunomodulators Registry (BADBIR), with 1 year apremilast data now available following its inclusion.[5] 1. [redacted]	Comment noted. Further rationale for the exclusion of apremilast and dimethyl fumarate has been added. Please see section 3.5 of the final appraisal document. Regarding the effectiveness of apremilast, it was included in the 12-16 week network meta-analysis. The committee was presented with the results of this analysis in the first appraisal committee meeting (November 2018).

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			2. https://www.nice.org.uk/guidance/ta419 3. Kleyn et al. UK and Ireland Real-World Experience With Apremilast in Psoriasis Patients: Analysis of 126 Patients From the APPRECIATE Study. 2018 4. Shams et al. Quality of Life and Patient Satisfaction in an Apremilast-Treated Psoriasis Population: Analysis of 126 Patients From the APPRECIATE Study in the United Kingdom and Ireland. 2018 http://www.badbir.org/	
11	Commentator	LEO Pharma	We agree with the committees decision that infliximab is a relevant comparator as it has been for other biological agents in psoriasis.	Comment noted.
12	Commentator	LEO Pharma	We disagree that Apremilast and dimethyl fumarate are not relevant comparators for this appraisal. Both these agents have been positioned by NICE, for use in the same group of patients where the currently approved biologics are being used. As a result these treatments have been included in local guidelines for use as alternative to biologics in a number of areas. The most recent technological appraisals (STAs) for Brodalumab included these treatments as comparators (Guselkumab was a fast track appraisal so did not require comparison to all available treatments) , thus the Tildrakizumab appraisal should incorporate them as well for completeness. Alternatively NICE should review the recommendations for Dimethyl Fumarate and Apremilast to make it clear their use is only for patients who are severe but unsuitable for biologics.	Comment noted. Further rationale for the exclusion of apremilast and dimethyl fumarate has been added. Please see section 3.5 of the final appraisal document.
13	Commentator	LEO Pharma	We agree with the committees decision to include modelling of treatment-specific induction period costs as this reflects clinical practice and give a more accurate reflection of costs which can vary widely during induction.	Comment noted.
14	Commentator	LEO Pharma	The timeline applied to the stopping rule for already approved biologics have been consistent with the timings used to determine the primary end-point within their clinical trials. 28 weeks was not the time used to determine primary endpoint within the Tildrakizumab trials. Using the 28 weeks as the stopping rule is a very long period compared to other currently available biologics for the treatment of Psoriasis, to determine if a treatment is likely to be effective. If a recommendation is made in future for the use of Tildrakizumab, it should be made clear within the recommendations that other biological options with shorter more cost-effective induction periods exists and these should be considered prior to a decision to use Tildrakizumab.	Comment noted. Please see sections 1.2 and 3.11 of the final appraisal document.
15	Commentator	LEO Pharma	We agree with the proposal that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance.	Comment noted.
16	Commentator	Novartis	Has all of the relevant evidence been taken into account? Novartis considers that the relevant evidence has generally been taken into account by the Appraisal Committee in preparing the provisional recommendations detailed in the ACD. However, we urge further committee consideration on two aspects where we believe the evidence would support alternative decisions:	Comments noted. Further rationale for the exclusion of apremilast and dimethyl fumarate has been added. Please see section 3.5 of the final appraisal document.

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			1. Paragraph 3.5: “Apremilast and dimethyl fumarate are not relevant comparators to tildrakizumab”. a. The justification provided that these options are “rarely used in practice” is not supported by the evidence. HMSL (IQVIA syndicated patient record service) moving annual total (MAT) data to October 2018 indicates that almost [redacted] of patients starting a targeted systemic therapy (including biologics, apremilast and dimethyl fumarate) for the first time, started on apremilast (data provided as academic-in-confidence). Skilarence (dimethyl fumarate) is also used to a lesser extent, although this could be due to relatively recent NICE approval (TA475, September 2017).1 Furthermore as noted in TA475, other fumaric acid ester formulations (such as Fumaderm) “are already used as 'off-label' treatments for psoriasis in the NHS”, hence dimethyl fumarate should be considered part of UK clinical practice. Moreover, other therapies recently approved by NICE, such as brodalumab (TA511)2 and guselkumab (TA521)3are rarely used in practice currently, and this has not prevented them from being considered relevant comparators. b. Additionally, the NICE recommendations for apremilast and dimethyl fumarate are identical to those of the biologic therapies (including adalimumab, brodalumab, etanercept, guselkumab, infliximab, ixekizumab, secukinumab and ustekinumab) in terms of specifying that patients should have failed to respond to methotrexate, ciclosporin and PUVA. All of these options are described as “fourth line” treatments in paragraph 3.2 of the ACD. The only standard technology appraisal published in plaque psoriasis since the approval of Skilarence, is brodalumab (TA511).2 Within the brodalumab appraisal apremilast and dimethyl fumarate were considered relevant comparators. We therefore see no rationale for excluding apremilast and dimethyl fumarate as relevant comparators to tildrakizumab. c. Furthermore, both apremilast and dimethyl fumarate were specified in the final scope for this appraisal as relevant comparators within the population of patients for whom conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated. d. Finally, the conclusion that apremilast and dimethyl fumarate are not relevant comparators to a new biologic potentially sets a precedent that these oral options form a separate step in the treatment pathway, ahead of biologic therapies. This would be contrary to the marketing authorisations of apremilast versus many of the biologic therapies. The apremilast licence states that it is “indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA)”.4 This contrasts with the licensed indications for several of the biologic therapies (including adalimumab, brodalumab, certolizumab pegol, guselkumab, ixekizumab, secukinumab and tildrakizumab), which do not specify that patients should have failed to respond to methotrexate, ciclosporin or PUVA but instead state that they are for use in	Regarding assessing response to tildrakizumab please see sections 1.2 and 3.11 of the final appraisal document.

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			patients who are “candidates for systemic therapy”.5 Therefore, based on the EMA marketing authorisation, many of the biologic therapies are for use earlier in the treatment pathway than apremilast. It would therefore be inappropriate for NICE to be perceived to position apremilast ahead of biologic therapies. Therefore we do not consider that adequate justification has been provided in support of the decision to exclude apremilast and dimethyl fumarate as relevant comparators. 2. Paragraph 3.10 “Tildrakizumab treatment response should be assessed at 28 weeks“. The rationale for this decision appears to relate to the tildrakizumab marketing authorisation which specifies 28 weeks as an appropriate timepoint to consider discontinuation amongst non-responders, because an increase in tildrakizumab PASI 75 response rates is observed between 12 and 28 weeks, and because of the 12-weekly dosing of tildrakizumab. However; a. There is precedent from the NICE appraisal of ixekizumab in moderate to severe psoriasis, for recommendations to differ versus the marketing authorisation in terms of appropriate timing of response assessment. Whilst the ixekizumab marketing authorisation states that “consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment”,6 the NICE recommendation (TA442) states “Stop ixekizumab treatment at 12 weeks if the psoriasis has not responded adequately”.7 b. Increases in efficacy are also observed with secukinumab and other biologics beyond the NICE recommended timepoint for assessment of response.8,9 c. Ustekinumab is also dosed at weeks 0, 4 and 12-weekly thereafter10, and the NICE recommendation nevertheless states that response should be assessed at 16 weeks (TA180).11 Therefore, we do not consider that sufficient justification has been provided in support of the decision that the appropriate timepoint for assessment of response to tildrakizumab should be 28 weeks. **References** 1. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA475]. Dimethyl fumarate for treating moderate to severe plaque psoriasis. September 2017. 2. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA511]. Brodalumab for treating moderate to severe plaque psoriasis. March 2018. 3. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA521]. Guselkumab for treating moderate to severe plaque psoriasis. June 2018. 4. European Medicines Agency (EMA). Otezla 10 mg / 20 mg / 30 mg film-coated tablets Summary of Product Characteristics. Available at https://www.ema.europa.eu/documents/product-information/otezla-epar-	

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			product-information_en.pdf Last accessed 18th December 2018. 5. European Medicines Agency (EMA). Cosentyx 150 mg powder for solution for injection. Summary of Product Characteristics. Available at https://www.ema.europa.eu/documents/product-information/cosentyx-epar-product-information_en.pdf Last accessed 18th December 2018. 6. European Medicines Agency (EMA). Taltz 80 mg solution for injection in pre-filled syringe. Summary of Product Characteristics. Available at https://www.ema.europa.eu/documents/product-information/taltz-epar-product-information_en.pdf Last accessed 18th December 2018. 7. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA442]. Ixekizumab for treating moderate to severe plaque psoriasis. April 2017. 8. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, Puig L, Nakagawa H, Spelman L, Sigurgeirsson B, Rivas E. Secukinumab in plaque psoriasis—results of two phase 3 trials. New England Journal of Medicine. 2014 Jul 24;371(4):326-38. 9. Langley RG, Tsai TF, Flavin S, Song M, Randazzo B, Wasfi Y, Li S, Puig L. efficacy of switching from ustekinumab to guselkumab in patients with moderate-to-severe plaque psoriasis: Results from the Navigate study: 4915. Journal of the American Academy of Dermatology. 2017 Jun 1;76(6):AB120. 10. European Medicines Agency (EMA). Stelara 45 mg / 90 mg solution for injection. Summary of Product Characteristics. Available at https://www.ema.europa.eu/documents/product-information/stelara-epar-product-information_en.pdf Last accessed 19th December 2018. 11. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA180]. Ustekinumab for the treatment of moderate to severe plaque psoriasis. September 2009.	
17	Commentator	Novartis	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Novartis considers the summaries of clinical and cost-effectiveness in the ACD to be, on the whole, reasonable interpretations of the evidence. However, we query the factual accuracy of the statement within paragraph 3.13, that “patients moved to the best supportive care state between treatments in a sequence”. Neither the manufacturer’s submission (section 3.2) or the ERG report (section 5.2.2) mention this.	The text has been corrected. Please see section 3.14 of the final appraisal document. The appraisal consultation document incorrectly stated that ‘Patients moved to the best supportive care state between treatments in a sequence or if their psoriasis did not respond to the last active treatment in a sequence’ (section 3.13 of the ACD). This error has been corrected to reflect that patients in the model moved to best supportive care only if psoriasis did not respond to the last active therapy in a treatment sequence.
18	Public	NHS Professional	"Place in treatment pathway - ie sequential treatment We would appreciate clear guidance as to where in the treatment pathway the technology should sit (1st, 2nd or 3rd line). "	Comment noted. Please see section 3.3 of the final appraisal document.
19	Public	NHS Professional	"(2) Dosing schedule - 100mg vs 200mg We would appreciate clear criteria in relation to dose escalation. The SPC states	Comment noted. Please see section 3.8 of the final appraisal document. The text is consistent with the

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			that patients with high disease burden or bodyweight over 90kg may benefit from 200mg, but the clinical trials cohort appear to be similar in both groups. There should be clear criteria for each dosing regimen to reduce risk of 'overtreatment'."	Summary of Product Characteristics.
20	Public	NHS Professional	"Pre-biologic treatment - PUVA There are debates about the need for PUVA as per all NICE TAs (excluding Infliximab). Practice across the area varies. Local clinicians consider PUVA as not appropriate for most of their patients and would use UVB instead. However, this is not in line with BAD guidelines and NICE CG. Is the use of PUVA reflective of clinical practice? "	The text has been amended to reflect this. Please see sections 1.1 and 3.2 of the final appraisal document.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
[ID1060] tildrakizumab - ACD comments David Chandler - 071218.doc	Psoriasis and Psoriatic Arthritis Alliance	None	4	
[ID1060] tildrakizumab - ACD stakeholder comments BAD- 030119.doc	[British Association of Dermatologists]	[N/A]	2	

NICE National Institute for Health and Care Excellence

Tildrakizumab for treating chronic plaque psoriasis after systemic therapy [ID1060]

Consultation on the appraisal consultation document – deadline for comments 5pm on **4 January 2019 email:** TACommB@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Almirall**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Not applicable**
Name of commentator person completing form:	[redacted]

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1	Almirall appreciate the opportunity to respond to the Appraisal Consultation Document (ACD) for tildrakizumab for treating adults with moderate to severe plaque psoriasis for whom systemic treatment is appropriate. We confirm that all the relevant evidence has been taken into account and the summaries of clinical and cost-effectiveness are reasonable interpretations of that evidence. We are disappointed that the provisional recommendations do not recommend tildrakizumab particularly since the unmet need for additional treatment options in this group of patients is clearly recognised (ACD section 3.2)
2	With the agreement of NICE, we have submitted additional cost-effectiveness estimates (as a separate document) to address the points raised by the Appraisal Committee (ACD Section 3.23). We hope that the additional cost-effectiveness analyses provided will enable the Committee to recommend tildrakizumab as a cost-effective option following the second Appraisal Committee meeting.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Psoriasis and Psoriatic Arthritis Alliance**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Although is it always going to be disappointing to people with psoriasis to see that a new therapy for their disease will not be routinely available as part the treatment pathway, we accept that any new therapy must be cost-effective to the NHS.
2	It is unfortunate that the data supplied for tildrakizumab did not provide sufficient evidence to help the committee make a positive recommendation.
3	As users of NHS services our constituent group want to have confidence in the therapies offered and as with other chronic conditions, need access to a wide range of therapies as efficacy wanes. Fortunately for psoriasis patients there are a number of similar therapies approved and available. So this decision is less urgent, but we would hope that the manufacturer will endeavour to provide the answers needed to allow the committee to reconsider this initial decision, as any additional choice is welcomed.
4	We believe as an organisation that as newer therapies become available for appraisal, patients deserve each subsequent therapy to provide substantial improvement on current therapies, if the product provides the same effectiveness, then it does appear reasonable for the NHS to seek a better commercial price, which will not only help those with psoriasis but others who also rely on cost effective treatments within the NHS.
5	
6	

Insert extra rows as needed

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- Do not use abbreviations
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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Association of Dermatologists**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**N/A**]
Name of commentator person completing form:	[[redacted] **on behalf of the British Association of Dermatologists' Therapy & Guidelines sub-committee**]

Comment number	**Comments** Insert each comment in a new row.

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NICE National Institute for Health and Care Excellence

Tildrakizumab for treating chronic plaque psoriasis after systemic therapy [ID1060]

Consultation on the appraisal consultation document – deadline for comments 5pm on **4 January 2019 email:** TACommB@nice.org.uk/NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	In relation to the discussion as to whether efficacy of tildrakizumab be assessed at 12 weeks or 28 weeks, in clinical practice it is not possible to keep a patient with severe disease on a drug for 7 months in hope of efficacy which is not materialising. In reality, a decision will be made far earlier than this (e.g. 12 weeks), based perhaps on lesser degrees of response. A model allowing continuation to 28 weeks to assess PASI75 in those who achieve a partial response (e.g. PASI50) earlier may be helpful
2	Experience with TNF and IL17 inhibitors have shown how important it is in practice to have more than one agent in a therapeutic class
3	The importance of 3 monthly injections (compared with monthly injections with the other licensed drug in this class) to patients and carers should be considered

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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NICE National Institute for Health and Care Excellence

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Celgene Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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Tildrakizumab for treating chronic plaque psoriasis after systemic therapy [ID1060]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Celgene does not agree with the conclusions reached in Section 3.5 of the ACD. The following points outline the reasoning for apremilast to be included as a relevant comparator during decision making. • Celgene has on-file market share data, which shows that the use of apremilast is established in NHS clinical practice, deeming it a relevant comparator as in line with the NICE Methods Guide.[1] Apremilast is also recommended by NICE in line with biologic therapies and dimethyl fumarate[2], and its use is expected to continue unless and until it is replaced by a new technology. • Conclusions drawn as to the perceived effectiveness of apremilast are also inaccurate. Apremilast is an established treatment in NHS clinical practice, with clinical advocacy, as well as real-world evidence supporting both its effectiveness and relevance as a comparator in NICE appraisals of technologies for treating moderate to severe plaque psoriasis.[3,4] • Apremilast is also an established treatment option for psoriasis in the British Association of Dermatologists Biologics and Immunomodulators Registry (BADBIR), with 1 year apremilast data now available following its inclusion.[5] 1. [redacted] 2. https://www.nice.org.uk/guidance/ta419 3. Kleyn et al. UK and Ireland Real-World Experience With Apremilast in Psoriasis Patients: Analysis of 126 Patients From the APPRECIATE Study. 2018 4. Shams et al. Quality of Life and Patient Satisfaction in an Apremilast-Treated Psoriasis Population: Analysis of 126 Patients From the APPRECIATE Study in the United Kingdom and Ireland. 2018 5. http://www.badbir.org/
2	
3	
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Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[LEO Pharma
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[N/A]
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We agree with the committees decision that infliximab is a relevant comparator as it has been for other biological agents in psoriasis.
2	We disagree that Apremilast and dimethyl fumarate are not relevant comparators for this appraisal. Both these agents have been positioned by NICE, for use in the same group of patients where the currently approved biologics are being used. As a result these treatments have been included in local guidelines for use as alternative to biologics in a number of areas. The most recent technological appraisals (STAs) for Brodalumab included these treatments as comparators (Guselkumab was a fast track appraisal so did not require comparison to all available treatments) , thus the Tildrakizumab appraisal should incorporate them as well for completeness. Alternatively NICE should review the recommendations for Dimethyl Fumarate and Apremilast to make it clear their use is only for patients who are severe but unsuitable for biologics.
3	We agree with the committees decision to include modelling of treatment-specific induction period costs as this reflects clinical practice and give a more accurate reflection of costs which can vary widely during induction.
4	The timeline applied to the stopping rule for already approved biologics have been consistent with the timings used to determine the primary end-point within their clinical trials. 28 weeks was not the time used to determine primary endpoint within the Tildrakizumab trials. Using the 28 weeks as the stopping rule is a very long period compared to other currently available biologics for the treatment of Psoriasis, to determine if a treatment is likely to be effective. If a recommendation is made in future for the use of Tildrakizumab, it should be made clear within the recommendations that other biological options with shorter more cost-effective induction periods exists and these should be considered prior to a decision to use Tildrakizumab.
5	We agree with the proposal that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance.
6	

Insert extra rows as needed

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NOVARTIS

Novartis Pharmaceuticals UK Limited
Frimley Business Park
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Surrey
GU16 7SR

Ms H Knight
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
1st Floor 10 Spring Gardens
London
SW1A 2BU

4th January 2019

Dear Ms Knight,

Re: Tildrakizumab for treating moderate to severe plaque psoriasis [ID1060] – Appraisal Consultation Document

Thank you for your letter dated 27th November inviting comments on the Appraisal Consultation Document (ACD) for the above appraisal.

This document answers the four questions posed by NICE on page 1 of the ACD.

Has all of the relevant evidence been taken into account?

Novartis considers that the relevant evidence has generally been taken into account by the Appraisal Committee in preparing the provisional recommendations detailed in the ACD.

However, we urge further committee consideration on two aspects where we believe the evidence would support alternative decisions:

1. Paragraph 3.5: “Apremilast and dimethyl fumarate are not relevant comparators to tildrakizumab”.
    a. The justification provided that these options are “rarely used in practice” is not supported by the evidence. HMSL (IQVIA syndicated patient record service) moving annual total (MAT) data to October 2018 indicates that almost [redacted] of patients starting a targeted systemic therapy (including biologics, apremilast and dimethyl fumarate) for the first time, started on apremilast (data provided as academic-in-confidence). Skilarence (dimethyl fumarate) is also used to a lesser extent, although this could be due to relatively recent NICE approval (TA475, September 2017).[1] Furthermore as noted in TA475, other fumaric acid ester formulations (such as Fumaderm) “are already used as 'off-label'

treatments for psoriasis in the NHS", hence dimethyl fumarate should be considered part of UK clinical practice. Moreover, other therapies recently approved by NICE, such as brodalumab (TA511)[2] and guselkumab (TA521)[3]are rarely used in practice currently, and this has not prevented them from being considered relevant comparators.

b. Additionally, the NICE recommendations for apremilast and dimethyl fumarate are identical to those of the biologic therapies (including adalimumab, brodalumab, etanercept, guselkumab, infliximab, ixekizumab, secukinumab and ustekinumab) in terms of specifying that patients should have failed to respond to methotrexate, ciclosporin and PUVA. All of these options are described as "fourth line" treatments in paragraph 3.2 of the ACD. The only standard technology appraisal published in plaque psoriasis since the approval of Skilarence, is brodalumab (TA511).[2] Within the brodalumab appraisal apremilast and dimethyl fumarate were considered relevant comparators. We therefore see no rationale for excluding apremilast and dimethyl fumarate as relevant comparators to tildrakizumab.
c. Furthermore, both apremilast and dimethyl fumarate were specified in the final scope for this appraisal as relevant comparators within the population of patients for whom conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated.
d. Finally, the conclusion that apremilast and dimethyl fumarate are not relevant comparators to a new biologic potentially sets a precedent that these oral options form a separate step in the treatment pathway, ahead of biologic therapies. This would be contrary to the marketing authorisations of apremilast versus many of the biologic therapies. The apremilast licence states that it is "indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA)".[4] This contrasts with the licensed indications for several of the biologic therapies (including adalimumab, brodalumab, certolizumab pegol, guselkumab, ixekizumab, secukinumab and tildrakizumab), which do not specify that patients should have failed to respond to methotrexate, ciclosporin or PUVA but instead state that they are for use in patients who are "candidates for systemic therapy".[5] Therefore, based on the EMA marketing authorisation, many of the biologic therapies are for use earlier in the treatment pathway than apremilast. It would therefore be inappropriate for NICE to be perceived to position apremilast ahead of biologic therapies.

Therefore we do not consider that adequate justification has been provided in support of the decision to exclude apremilast and dimethyl fumarate as relevant comparators.

2. Paragraph 3.10 "Tildrakizumab treatment response should be assessed at 28 weeks". The rationale for this decision appears to relate to the tildrakizumab marketing authorisation which specifies 28 weeks as an appropriate timepoint to consider discontinuation amongst non-responders, because an increase in

tildrakizumab PASI 75 response rates is observed between 12 and 28 weeks, and because of the 12-weekly dosing of tildrakizumab. However;

a. There is precedent from the NICE appraisal of ixekizumab in moderate to severe psoriasis, for recommendations to differ versus the marketing authorisation in terms of appropriate timing of response assessment. Whilst the ixekizumab marketing authorisation states that "consideration should be given to discontinuing treatment in patients who have shown no response after **16 to 20** weeks of treatment",[6] the NICE recommendation (TA442) states "Stop ixekizumab treatment at **12** weeks if the psoriasis has not responded adequately".[7]
b. Increases in efficacy are also observed with secukinumab and other biologics beyond the NICE recommended timepoint for assessment of response.[8,9]
c. Ustekinumab is also dosed at weeks 0, 4 and 12-weekly thereafter[10], and the NICE recommendation nevertheless states that response should be assessed at 16 weeks (TA180).[11]

Therefore, we do not consider that sufficient justification has been provided in support of the decision that the appropriate timepoint for assessment of response to tildrakizumab should be 28 weeks.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Novartis considers the summaries of clinical and cost-effectiveness in the ACD to be, on the whole, reasonable interpretations of the evidence.

However, we query the factual accuracy of the statement within paragraph 3.13, that "patients moved to the best supportive care state between treatments in a sequence". Neither the manufacturer's submission (section 3.2) or the ERG report (section 5.2.2) mention this.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Novartis has no comments.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Novartis does not have any comments in relation to the above potential equality issues.

I hope that our comments are of value. If you require clarification on any aspects of our response, please do not hesitate to contact me.

Yours sincerely,

[redacted]
[redacted]
Novartis Pharmaceuticals UK Ltd

References

1. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA475]. Dimethyl fumarate for treating moderate to severe plaque psoriasis. September 2017.
2. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA511]. Brodalumab for treating moderate to severe plaque psoriasis. March 2018.
3. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA521]. Guselkumab for treating moderate to severe plaque psoriasis. June 2018.
4. European Medicines Agency (EMA). Otezla 10 mg / 20 mg / 30 mg film-coated tablets Summary of Product Characteristics. Available at https://www.ema.europa.eu/documents/product-information/otezla-epar-product-information_en.pdf Last accessed 18th December 2018.
5. European Medicines Agency (EMA). Cosentyx 150 mg powder for solution for injection. Summary of Product Characteristics. Available at https://www.ema.europa.eu/documents/product-information/cosentyx-epar-product-information_en.pdf Last accessed 18th December 2018.
6. European Medicines Agency (EMA). Taltz 80 mg solution for injection in pre-filled syringe. Summary of Product Characteristics. Available at https://www.ema.europa.eu/documents/product-information/taltz-epar-product-information_en.pdf Last accessed 18th December 2018.
7. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA442]. Ixekizumab for treating moderate to severe plaque psoriasis. April 2017.
8. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, Puig L, Nakagawa H, Spelman L, Sigurgeirsson B, Rivas E. Secukinumab in plaque psoriasis—results of two phase 3 trials. New England Journal of Medicine. 2014 Jul 24;371(4):326-38.
9. Langley RG, Tsai TF, Flavin S, Song M, Randazzo B, Wasfi Y, Li S, Puig L. efficacy of switching from ustekinumab to guselkumab in patients with moderate-to-severe plaque psoriasis: Results from the Navigate study: 4915. Journal of the American Academy of Dermatology. 2017 Jun 1;76(6):AB120.
10. European Medicines Agency (EMA). Stelara 45 mg / 90 mg solution for injection. Summary of Product Characteristics. Available at https://www.ema.europa.eu/documents/product-information/stelara-epar-product-information_en.pdf Last accessed 19th December 2018.
11. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA180]. Ustekinumab for the treatment of moderate to severe plaque psoriasis. September 2009.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	SWL Commissioning Pharmacist
Organisation	NEL (formerly NEL CSU)
Location	England
Conflict	No
Notes	

Comments the ACD:

"Place in treatment pathway - ie sequential treatment
We would appreciate clear guidance as to where in the treatment pathway the technology should sit (1st, 2nd or 3rd line). "
"(2) Dosing schedule - 100mg vs 200mg
We would appreciate clear criteria in relation to dose escalation. The SPC states that patients with high disease burden or bodyweight over 90kg may benefit from 200mg, but the clinical trials cohort appear to be similar in both groups. There should be clear criteria for each dosing regimen to reduce risk of 'overtreatment'."
"Pre-biologic treatment - PUVA
There are debates about the need for PUVA as per all NICE TAs (excluding Infliximab). Practice across the area varies. Local clinicians consider PUVA as not appropriate for most of their patients and would use UVB instead. However, this is not in line with BAD guidelines and NICE CG. Is the use of PUVA reflective of clinical practice? "

ID1060 – Tildrakizumab for treating moderate to severe plaque psoriasis

Almirall response to ACD consultation – 21st December 2018

Almirall appreciate the opportunity to respond to the Appraisal Consultation Document (ACD) and to submit additional cost-effectiveness analyses to address the points raised by the Appraisal Committee. We hope that the additional analyses will enable the Committee to recommend tildrakizumab as a cost-effective option following the second Appraisal Committee meeting.

Summary of revisions

In the revised base case the preferences of the Committee and ERG have been taken into account and the analysis has been designed to match the alternative ERG base case. This includes the additional assumption regarding utility reverting to baseline when patients receive best supportive care (BSC). (Note: The results for this scenario when implemented by the ERG were presented in Table 55 of the ERG report).

In addition, we have applied a revised and approved Patient Access Scheme (PAS) providing a simple discount of [redacted]. Taking this PAS into consideration the price per pack is [redacted] for both 100mg and 200mg doses.

A summary of the changes that have been implemented to the model are as follows:

- The inclusion of infliximab and hence the adoption of the network-meta analysis (NMA) (random effect without placebo adjusted) that included infliximab (ACD section 3.11).
- The inclusion of 14-week and 28-week tildrakizumab as separate interventions in the analysis (ACD section 3.16)
- The alteration of the induction and maintenance costs for the comparators (ACD section 3.15)
- The adoption of BSC costs from the Fonia *et al* study, equating to costs per cycle of £1,422 (ACD section 3.20)
- The removal of age-adjusted utilities (i.e. constant utilities) (ACD section 3.17)
- The use of the baseline utility value (0.61) for all patients receiving BSC (ACD section 3.18)
- The inclusion of the cost of non-responders (£801.50) (ACD section 3.19)

The ERG also stated a preference for a pairwise analysis, in which all interventions were compared directly to BSC with the interventions then ranked by net monetary benefit (NMB) with the highest ranked intervention deemed to be the most cost-effective option. Therefore, the focus of the revised analysis is a pairwise analysis. However, in the ACD (Section 3.14) it also states that *"[t]he committee agreed that, in principle, it was appropriate to compare treatment sequences in this appraisal*". Therefore, the results with a sequence approach are also presented.

It was noted in the ACD (Section 3.23) that *"[t]he committee considered whether tildrakizumab would be a cost-effective use of NHS resources for people with severe psoriasis for whom biological treatments are an option, taking into account the patient access schemes associated with brodalumab, guselkumab, ixekizumab and secukinumab*." Therefore, for the purpose of

our analysis, it has been assumed that it would be more informative to present results with a PAS assumption implemented for each of the comparators just listed, rather than results for these comparators at list price (as was adopted for the original company submission). To account for potentially substantive but confidential PASs, two different levels of discount have been modelled (see below) both of which represent a significant discount; and two sets of results are presented:

- A [redacted] PAS for brodalumab, guselkumab, ixekizumab and secukinumab (no PAS for all other comparators)
- A [redacted] PAS for brodalumab, guselkumab, ixekizumab and secukinumab (no PAS for all other comparators)

Other considerations

The analyses presented in the following section focus only on the 100mg dose of tildrakizumab on the basis that:

- The 100mg and 200mg doses of tildrakizumab are flat priced.
- The ERG considered (Section 5.2.12 ERG report) that the cost-effectiveness results using the 100mg dose are sufficiently generalisable to the 200mg dose.

Results for the 100mg dose which provide the most conservative estimate of tildrakizumab cost-effectiveness. Analyses for the 200mg dose are provided in Appendix A.

Since the Appraisal Committee meeting, NHS England has completed a tendering process for biosimilar adalimumab. This will change the landscape for biologic systemic therapies for psoriasis. The analyses presented here do not include any discount for biosimilar adalimumab as the level of discount is unknown, but from the NHS England press releases it is anticipated to be a highly significant level of discount. It seems likely that none of the currently recommended biologic treatments would prove cost-effective compared to a highly discounted price of biosimilar adalimumab. The analyses below focus on demonstrating the cost-effectiveness of tildrakizumab compared to the other original scope comparator biologic treatments, on the assumption that tildrakizumab will not displace the increased use of biosimilar adalimumab 550on grounds of cost.

Results of revised analyses

The results of the pairwise analysis are presented in Table 1 and Table 2 for PASs for relevant comparators, which offer a simple discount of [redacted] and [redacted] from list price respectively. These results show that when a [redacted] PAS is implemented for each of the relevant comparators:

- All comparators are cost-effective versus BSC alone with the exception of infliximab, and also ustekinumab at a £20,000 per QALY threshold
- The optimal treatment based on NMB (vs BSC alone) is tildrakizumab 100mg (28 weeks).

When the PASs are increased to [redacted] the rankings, based on the NMB values, change but tildrakizumab 100mg (28 weeks) remains the optimal treatment option.

The results of the sequence approach analysis are shown in Table 3 and Table 4. For this analysis, the model was set up to match that of the ERG's alternative base case with additional

utility assumption for BSC (the results of the ERGs base case were presented in Table 57 of the ERG report). This includes the use of equivalent sequences as were applied by the ERG for that analysis.

Table 3 presents a fully incremental ICER comparison when [redacted] PASs were implemented for the relevant comparators. The least costly sequence was the tildrakizumab 100mg (14 weeks) sequence (sequence 1) and there were seven interventions that were either dominated or extendedly dominated. Of the remaining sequences, the tildrakizumab 100mg (28 weeks) sequence (sequence 3) had the lowest ICER of £16,364, whilst ixekizumab (sequence 8) had an ICER of £73,067

Table 4 presents a fully incremental ICER comparison when [redacted] PASs are implemented for the relevant comparators. The least costly sequence was again the tildrakizumab 100mg (14 weeks) sequence (sequence 1) and there were seven interventions that were either dominated or extendedly dominated. Of the remaining sequences, the tildrakizumab 100mg (28 weeks) sequence (sequence 3) had the lowest ICER of £16,909, whilst the ixekizumab (sequence 8) had an ICER of £44,275. Therefore, across both the sequence analyses undertaken tildrakizumab 100mg (28 weeks) was the optimal treatment choice at cost-effectiveness thresholds of up to £30,000 per QALY. Furthermore, in the ACD (section 3.23) it was noted that when the brodalumab PAS was implemented in the original base case it dominated tildrakizumab. However, with the new PAS discount of [redacted] for tildrakizumab, using a sequence approach analysis the tildrakizumab 100mg sequence (and also 200mg) remain cost-effective over the brodalumab sequence when discounts of up to [redacted] are applied for brodalumab.

To further test the robustness of the results, one-way deterministic sensitivity analyses (DSA) were undertaken for both the pairwise and sequence approaches. The results are presented via a series of tornado diagrams in Appendix B and indicate that, in terms of the pairwise analyses, the key driver of NMB values is the cost of BSC. However, these results show that changes to this cost parameter affect each of the interventions in the same way (e.g. if the cost of BSC is lower then the NMB decreases for all interventions). The results of the DSA with the sequence approach suggest the key drivers of the results for this form of analysis are discontinuation rates with tildrakizumab and the first line comparator. When a [redacted] PAS is implemented while there are a few iterations in which tildrakizumab is no longer the optimal sequence, on the whole the changes implemented did not alter the direction of the results.

Conclusion

Across the all forms of the additional analyses undertaken (i.e. pairwise and sequence approaches), the results indicate that tildrakizumab 100mg (28 weeks) (and hence also 200mg) is more cost-effective than other biological treatments if the PASs for those treatments (i.e. brodalumab, guselkumab, ixekizumab and secukinumab) provide a discount of [redacted] or less. These analyses were undertaken using the preferences of both the ERG (as outlined in the ERG report) and the Committee (as outlined in the ACD).

Table 1: Results using 100mg tildrakizumab with new PAS – pairwise approach and [redacted] PAS for comparators (brodalumab, guselkumab, ixekizumab and secukinumab)

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
BSC	£106,598	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Etanercept	£114,562	[redacted]	[redacted]	[redacted]	£14,221	£3,236	3	£8,836	8
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£10,498	£8,077	2	£16,577	2
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£11,308	£8,779	1	£18,879	1
Adalimumab	£122,728	[redacted]	[redacted]	[redacted]	£19,202	£670	7	£9,070	7
Ustekinumab	£124,830	[redacted]	[redacted]	[redacted]	£20,718	-£632	9	£8,168	9
Guselkumab	£125,536	[redacted]	[redacted]	[redacted]	£17,374	£2,862	4	£13,762	4
Secukinumab	£126,161	[redacted]	[redacted]	[redacted]	£17,785	£2,437	5	£13,437	5
Ixekizumab	£127,361	[redacted]	[redacted]	[redacted]	£18,055	£2,237	6	£13,737	3
Brodalumab	£129,138	[redacted]	[redacted]	[redacted]	£19,600	£460	8	£11,960	6
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£35,111	-£14,355	10	-£4,855	10

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; INB: incremental net monetary benefit; QALY: quality adjusted life year; wk: week. NOTE: for etanercept and infliximab analyses utilised the lowest biosimilar price.

Table 2: Results using 100mg tildrakizumab with new PAS – pairwise approach and [redacted] PAS for comparators (brodalumab, guselkumab, ixekizumab and secukinumab)

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
BSC	£106,598	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Etanercept	£114,562	[redacted]	[redacted]	[redacted]	£14,221	£3,236	7	£8,836	8
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£10,498	£8,077	2	£16,577	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£11,308	£8,779	1	£18,879	1
Guselkumab	£122,269	[redacted]	[redacted]	[redacted]	£14,377	£6,129	3	£17,029	3
Adalimumab	£122,728	[redacted]	[redacted]	[redacted]	£19,202	£670	8	£9,070	7
Secukinumab	£122,830	[redacted]	[redacted]	[redacted]	£14,756	£5,768	4	£16,768	4
Ixekizumab	£123,857	[redacted]	[redacted]	[redacted]	£15,007	£5,741	5	£17,241	2
Ustekinumab	£124,830	[redacted]	[redacted]	[redacted]	£20,718	-£632	9	£8,168	9
Brodalumab	£125,485	[redacted]	[redacted]	[redacted]	£16,423	£4,113	6	£15,613	6
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£35,111	-£14,355	10	-£4,855	10

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; INB: incremental net monetary benefit; QALY: quality adjusted life year; wk: week. NOTE: for etanercept and infliximab analyses utilised the lowest biosimilar price.

Table 3: Results using 100mg tildrakizumab with new PAS – sequence approach and [redacted] PAS for comparators (brodalumab, guselkumab, ixekizumab and secukinumab)

Sequence	1st line	2nd line	3rd line	4th line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) fully incremental
1	TIL 100mg 14wk	UST	SEC	BSC	[redacted]	[redacted]	NA	NA	NA
2	ETA	UST	SEC	BSC	£144,006	[redacted]	[redacted]	[redacted]	Dominated
3	TIL 100mg 28wk	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£16,364
4	ADA	UST	SEC	BSC	£150,900	[redacted]	[redacted]	[redacted]	Dominated
5	SEC	UST	ADA	BSC	£151,071	[redacted]	[redacted]	[redacted]	Dominated
6	UST	ADA	SEC	BSC	£151,429	[redacted]	[redacted]	[redacted]	Dominated
7	GUS	UST	SEC	BSC	£152,667	[redacted]	[redacted]	[redacted]	Extendedly dominated
8	IXE	UST	SEC	BSC	£154,223	[redacted]	[redacted]	[redacted]	£73,067
9	BRO	UST	SEC	BSC	£155,999	[redacted]	[redacted]	[redacted]	Dominated
10	INF	UST	SEC	BSC	£167,750	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA: adalimumab; BRO: brodalumab; BSC: best supportive care; ETA: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; N/A: not available; PAS: Patient Access Scheme; QALY: quality-adjusted life year; SEC: secukinumab; TIL: tildrakizumab; UST: ustekinumab; wk: week.
NOTE: for etanercept and infliximab analyses utilised the lowest biosimilar price.

Table 4: Results using 100mg tildrakizumab with new PAS – sequence approach and [redacted] PAS for comparators (brodalumab, guselkumab, ixekizumab and secukinumab)

Sequence	1st line	2nd line	3rd line	4th line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) fully incremental
1	TIL 100mg 14wk	UST	SEC	BSC	[redacted]	[redacted]	NA	NA	NA
2	ETA	UST	SEC	BSC	£141,519	[redacted]	[redacted]	[redacted]	Dominated
3	TIL 100mg 28wk	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£16,909
7	GUS	UST	SEC	BSC	£147,113	[redacted]	[redacted]	[redacted]	Extendedly dominated
5	SEC	UST	ADA	BSC	£147,740	[redacted]	[redacted]	[redacted]	Dominated
8	IXE	UST	SEC	BSC	£148,454	[redacted]	[redacted]	[redacted]	£44,275
4	ADA	UST	SEC	BSC	£148,523	[redacted]	[redacted]	[redacted]	Dominated
6	UST	ADA	SEC	BSC	£149,052	[redacted]	[redacted]	[redacted]	Dominated
9	BRO	UST	SEC	BSC	£150,083	[redacted]	[redacted]	[redacted]	Dominated
10	INF	UST	SEC	BSC	£165,405	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA: adalimumab; BRO: brodalumab; BSC: best supportive care; ETA: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; N/A: not available; PAS: Patient Access Scheme; QALY: quality-adjusted life year; SEC: secukinumab; TIL: tildrakizumab; UST: ustekinumab; wk: week.
NOTE: for etanercept and infliximab analyses utilised the lowest biosimilar price.

Appendix A – Results of base case analysis with 200mg tildrakizumab

Table A1: Results using 200mg tildrakizumab with new PAS – pairwise approach and [redacted] PAS for comparators (brodalumab, guselkumab, ixekizumab and secukinumab)

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
BSC	£106,598	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Etanercept	£114,856	[redacted]	[redacted]	[redacted]	£14,082	£3,470	3	£9,334	8
Tildrakizumab 200mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£10,287	£8,666	2	£17,589	2
Tildrakizumab 200mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£11,082	£9,496	1	£20,145	1
Adalimumab	£123,268	[redacted]	[redacted]	[redacted]	£18,887	£982	7	£9,809	7
Ustekinumab	£125,411	[redacted]	[redacted]	[redacted]	£20,433	-£399	9	£8,809	9
Guselkumab	£126,163	[redacted]	[redacted]	[redacted]	£17,195	£3,192	4	£14,571	4
Secukinumab	£126,793	[redacted]	[redacted]	[redacted]	£17,606	£2,747	5	£14,218	5
Ixekizumab	£128,023	[redacted]	[redacted]	[redacted]	£17,755	£2,709	6	£14,776	3
Brodalumab	£130,005	[redacted]	[redacted]	[redacted]	£19,398	£727	8	£12,794	6
Infliximab	£141,079	[redacted]	[redacted]	[redacted]	£34,549	-£14,521	10	-£4,540	10

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; INB: incremental net monetary benefit; QALY: quality adjusted life year; wk: week. NOTE: for etanercept and infliximab analyses utilised the lowest biosimilar price.

Table A2: Results using 200mg tildrakizumab with new PAS – pairwise approach and [redacted] PAS for comparators (brodalumab, guselkumab, ixekizumab and secukinumab)

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
BSC	£106,598	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Etanercept	£114,856	[redacted]	[redacted]	[redacted]	£14,082	£3,470	7	£9,334	8
Tildrakizumab 200mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£10,287	£8,666	2	£17,589	5
Tildrakizumab 200mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£11,082	£9,496	1	£20,145	1
Guselkumab	£122,778	[redacted]	[redacted]	[redacted]	£14,220	£6,577	3	£17,956	3
Adalimumab	£123,268	[redacted]	[redacted]	[redacted]	£18,887	£982	8	£9,809	7
Secukinumab	£123,343	[redacted]	[redacted]	[redacted]	£14,598	£6,197	5	£17,668	4
Ixekizumab	£124,394	[redacted]	[redacted]	[redacted]	£14,748	£6,338	4	£18,405	2
Ustekinumab	£125,411	[redacted]	[redacted]	[redacted]	£20,433	-£399	9	£8,809	9
Brodalumab	£126,211	[redacted]	[redacted]	[redacted]	£16,253	£4,521	6	£16,588	6
Infliximab	£141,079	[redacted]	[redacted]	[redacted]	£34,549	-£14,521	10	-£4,540	10

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; INB: incremental net monetary benefit; QALY: quality adjusted life year; wk: week. NOTE: for etanercept and infliximab analyses utilised the lowest biosimilar price.

Table A3: Results using 200mg tildrakizumab with new PAS – sequence approach and [redacted] PAS for comparators (brodalumab, guselkumab, ixekizumab and secukinumab)

Sequence	1st line	2nd line	3rd line	4th line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) fully incremental
1	TIL 200mg 14wk	UST	SEC	BSC	[redacted]	[redacted]	NA	NA	NA
2	ETA	UST	SEC	BSC	£145,127	[redacted]	[redacted]	[redacted]	Dominated
3	TIL 200mg 28wk	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£13,977
4	ADA	UST	SEC	BSC	£152,169	[redacted]	[redacted]	[redacted]	Dominated
5	SEC	UST	ADA	BSC	£152,314	[redacted]	[redacted]	[redacted]	Dominated
6	UST	ADA	SEC	BSC	£152,707	[redacted]	[redacted]	[redacted]	Dominated
7	GUS	UST	SEC	BSC	£153,942	[redacted]	[redacted]	[redacted]	Extendedly dominated
8	IXE	UST	SEC	BSC	£155,512	[redacted]	[redacted]	[redacted]	£82,355
9	BRO	UST	SEC	BSC	£157,494	[redacted]	[redacted]	[redacted]	Dominated
10	INF	UST	SEC	BSC	£169,576	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ADA: adalimumab; BRO: brodalumab; BSC: best supportive care; ETA: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; N/A: not available; PAS: Patient Access Scheme; QALY: quality-adjusted life year; SEC: secukinumab; TIL: tildrakizumab; UST: ustekinumab; wk: week. NOTE: for etanercept and infliximab analyses utilised the lowest biosimilar price.

Table A4: Results using 200mg tildrakizumab with new PAS – sequence approach and [redacted] PAS for comparators (brodalumab, guselkumab, ixekizumab and secukinumab)

Sequence	1st line	2nd line	3rd line	4th line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) fully incremental
1	TIL 200mg 14wk	UST	SEC	BSC	[redacted]	[redacted]	NA	NA	NA
2	ETA	UST	SEC	BSC	£142,571	[redacted]	[redacted]	[redacted]	Dominated
3	TIL 200mg 28wk	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£14,523
7	GUS	UST	SEC	BSC	£148,218	[redacted]	[redacted]	[redacted]	Extendedly dominated
5	SEC	UST	ADA	BSC	£148,864	[redacted]	[redacted]	[redacted]	Dominated
8	IXE	UST	SEC	BSC	£149,568	[redacted]	[redacted]	[redacted]	£49,800
4	ADA	UST	SEC	BSC	£149,732	[redacted]	[redacted]	[redacted]	Dominated
6	UST	ADA	SEC	BSC	£150,270	[redacted]	[redacted]	[redacted]	Dominated
9	BRO	UST	SEC	BSC	£151,385	[redacted]	[redacted]	[redacted]	Dominated
10	INF	UST	SEC	BSC	£167,174	[redacted]	[redacted]	[redacted]	Dominated

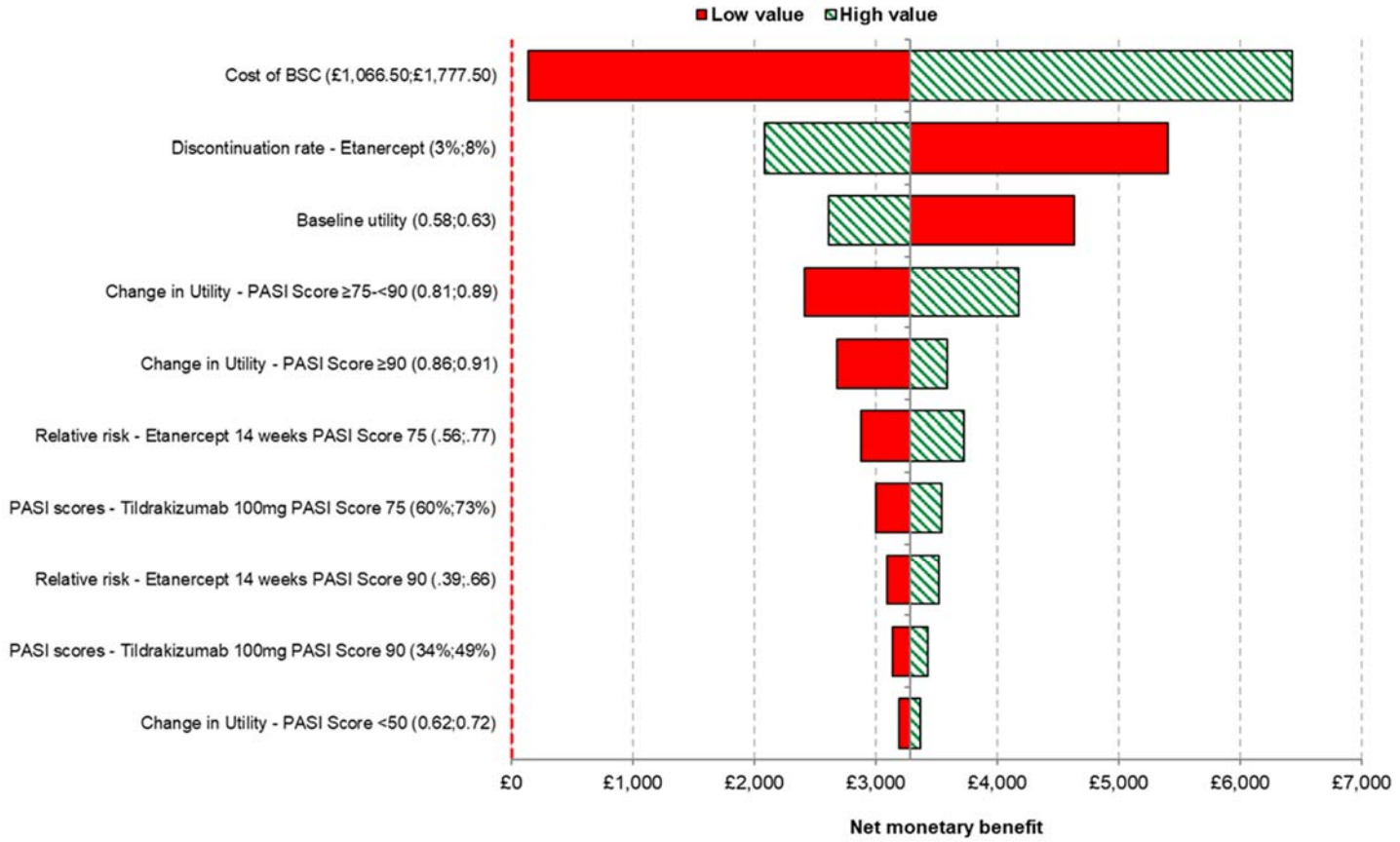
Abbreviations: ADA: adalimumab; BRO: brodalumab; BSC: best supportive care; ETA: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; IXE: ixekizumab; N/A: not available; PAS: Patient Access Scheme; QALY: quality-adjusted life year; SEC: secukinumab; TIL: tildrakizumab; UST: ustekinumab; wk: week.
NOTE: for etanercept and infliximab analyses utilised the lowest biosimilar price.

Appendix B: Results of one-way deterministic sensitivity analysis using tildrakizumab 100mg

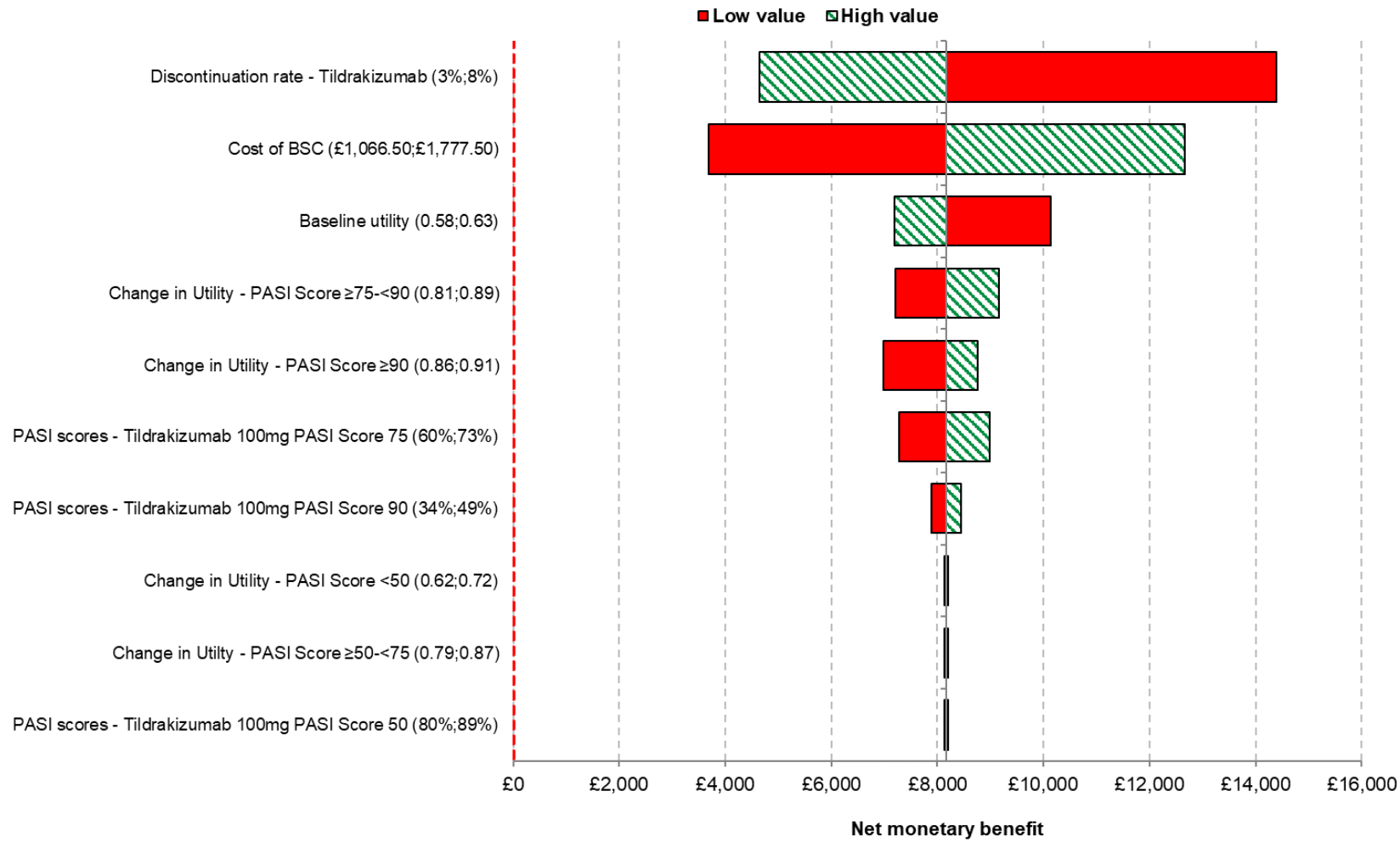
Results are presented for pairwise analysis (Figure B1), for sequence analysis using PAS discounts (for brodalumab, guselkumab, ixekizumab and secukinumab) of [redacted] (Figure B2) and [redacted] (Figure B3). For etanercept and infliximab all analyses utilised the lowest biosimilar price.

Figure B1 – pairwise analyses versus BSC

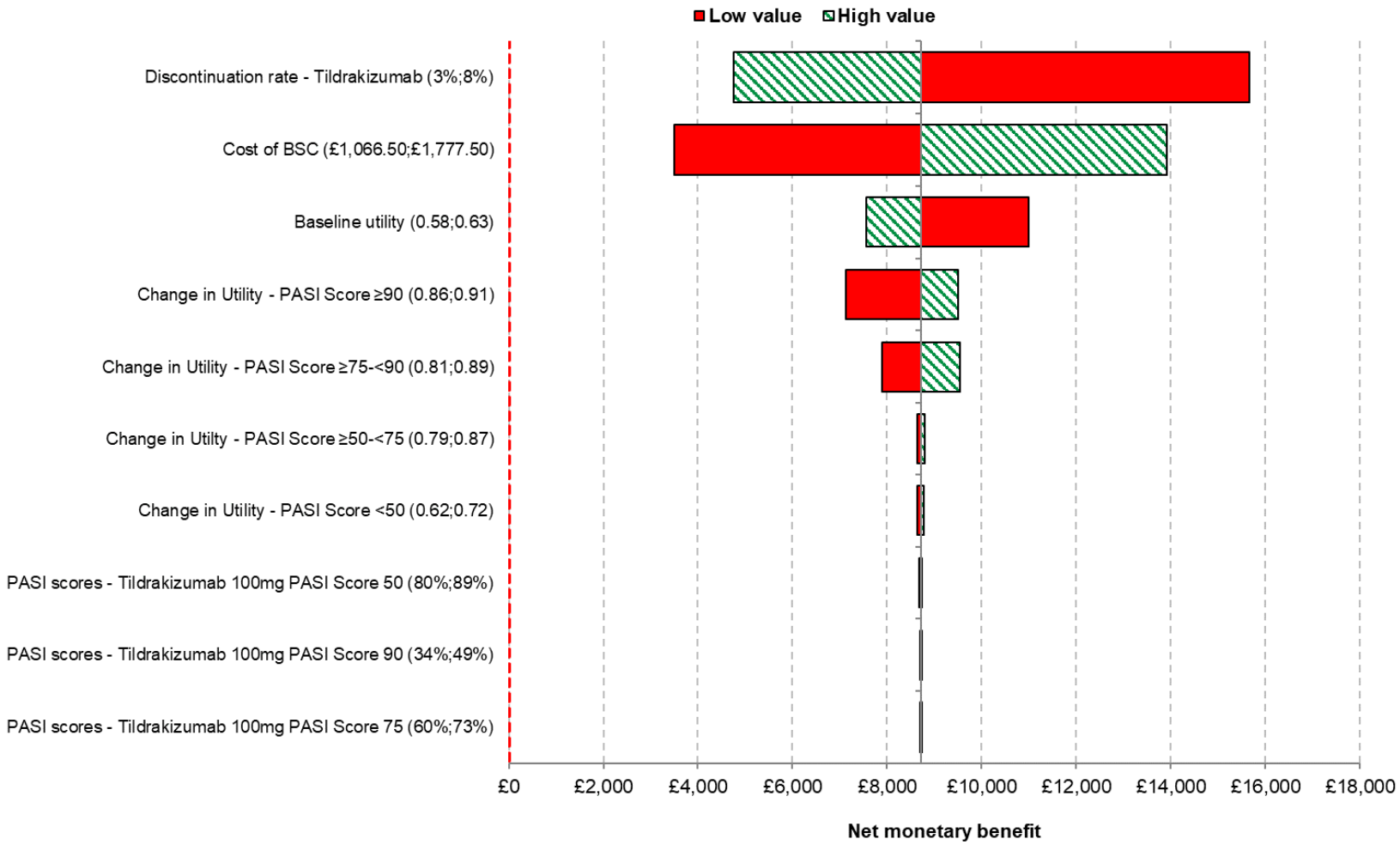
Etanercept (no PAS)



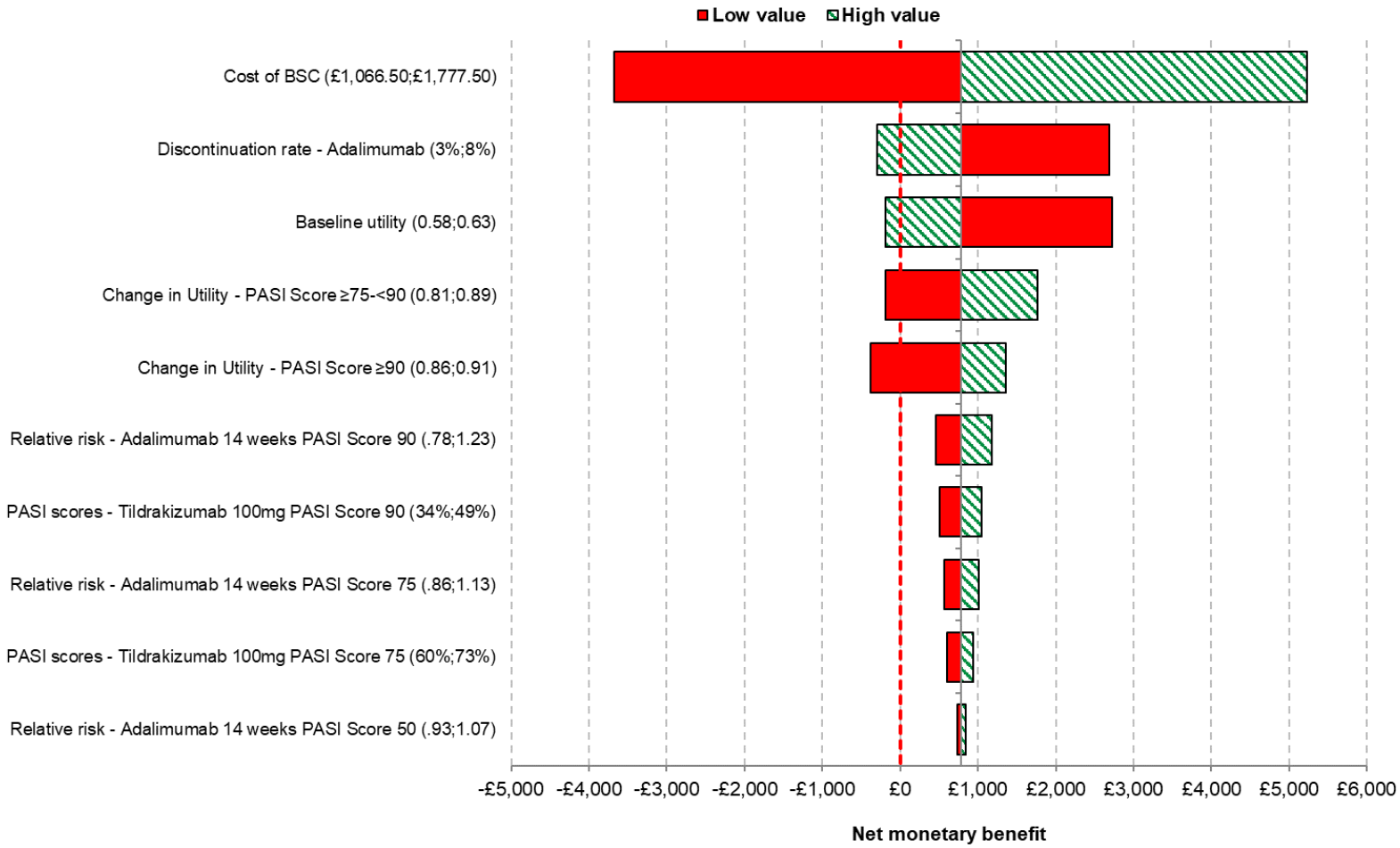
Tildrakizumab 14 weeks ([redacted] PAS)



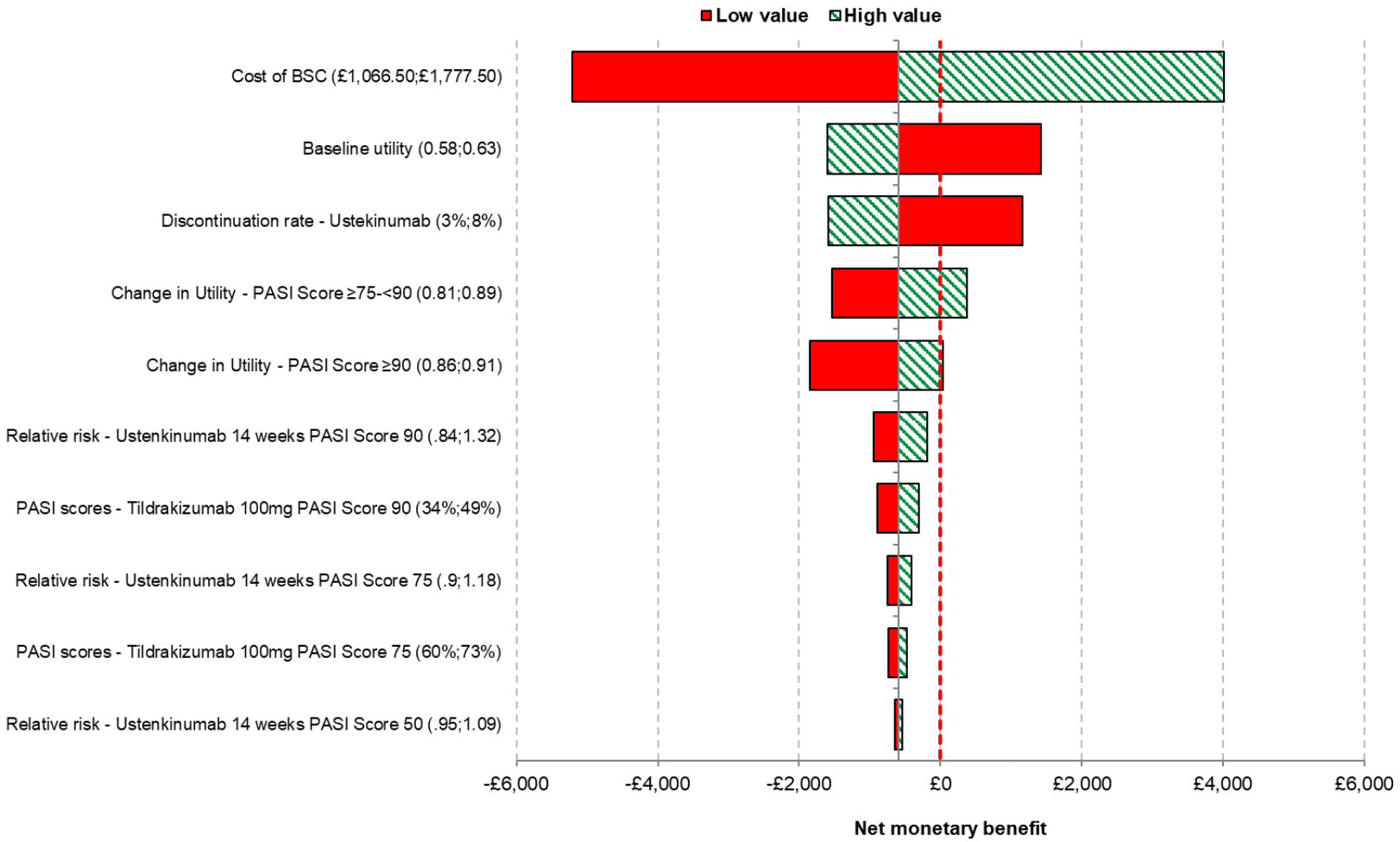
Tildrakizumab 100mg 28 weeks ([redacted] PAS)



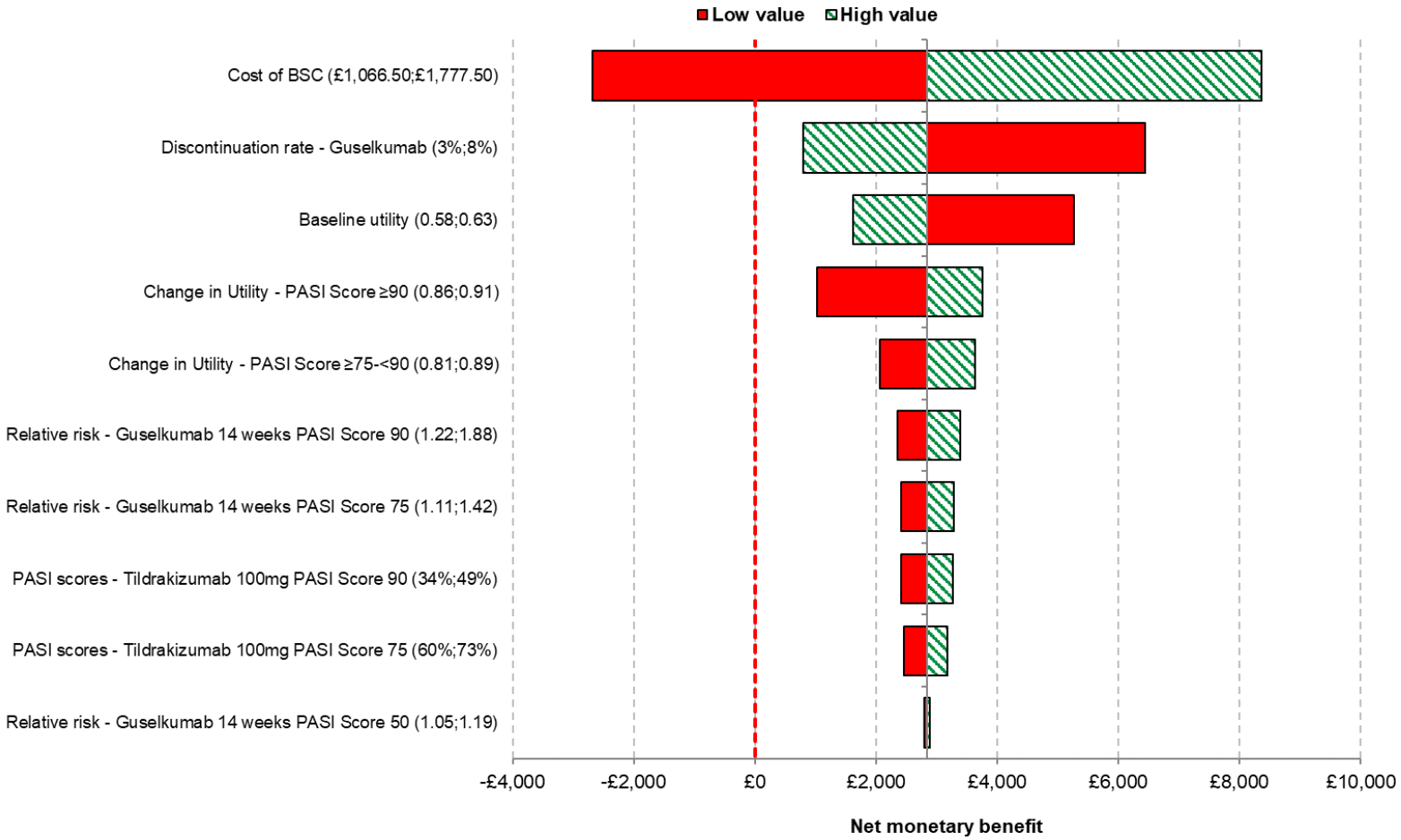
Adalimumab (no PAS)



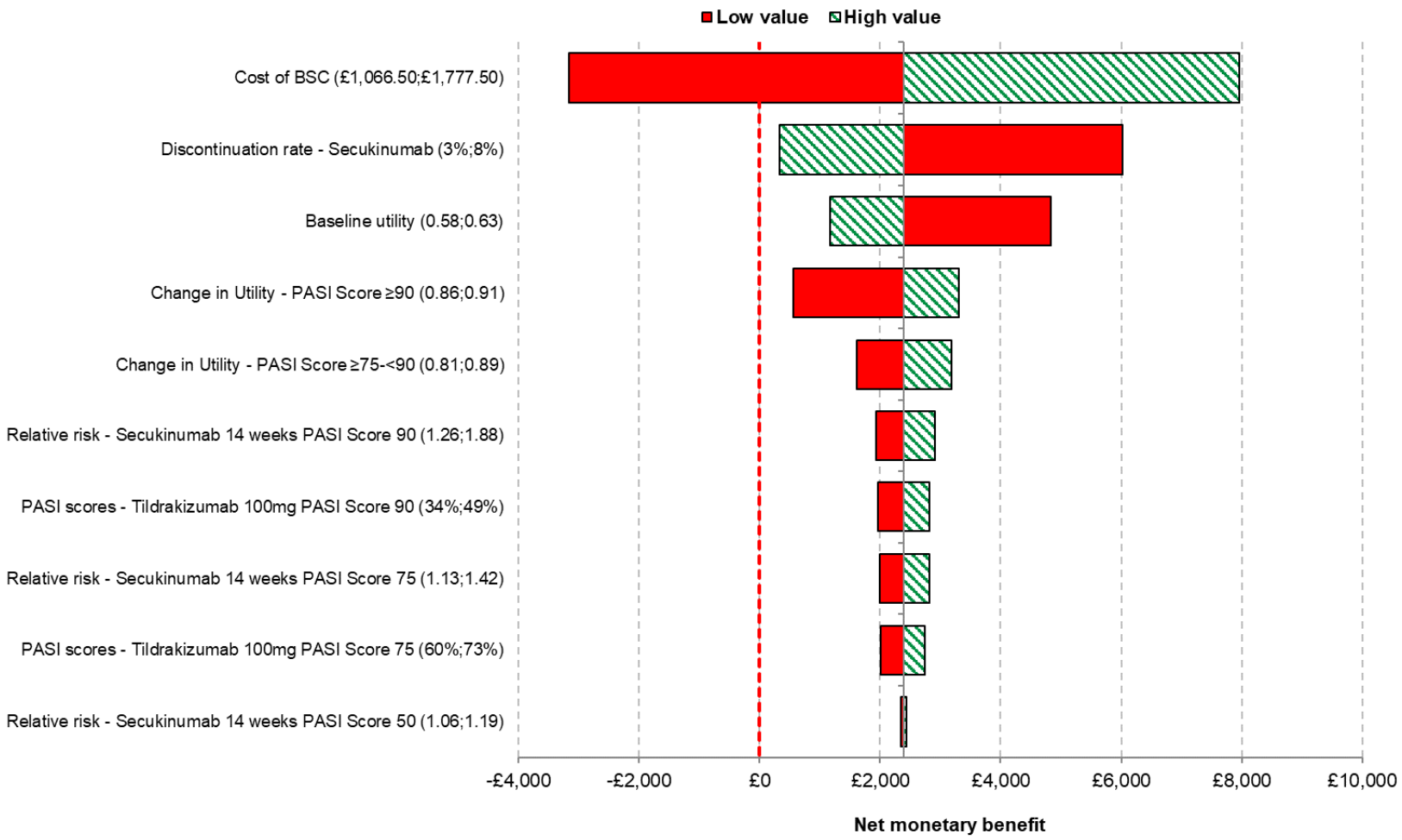
Ustekinumab (no PAS)



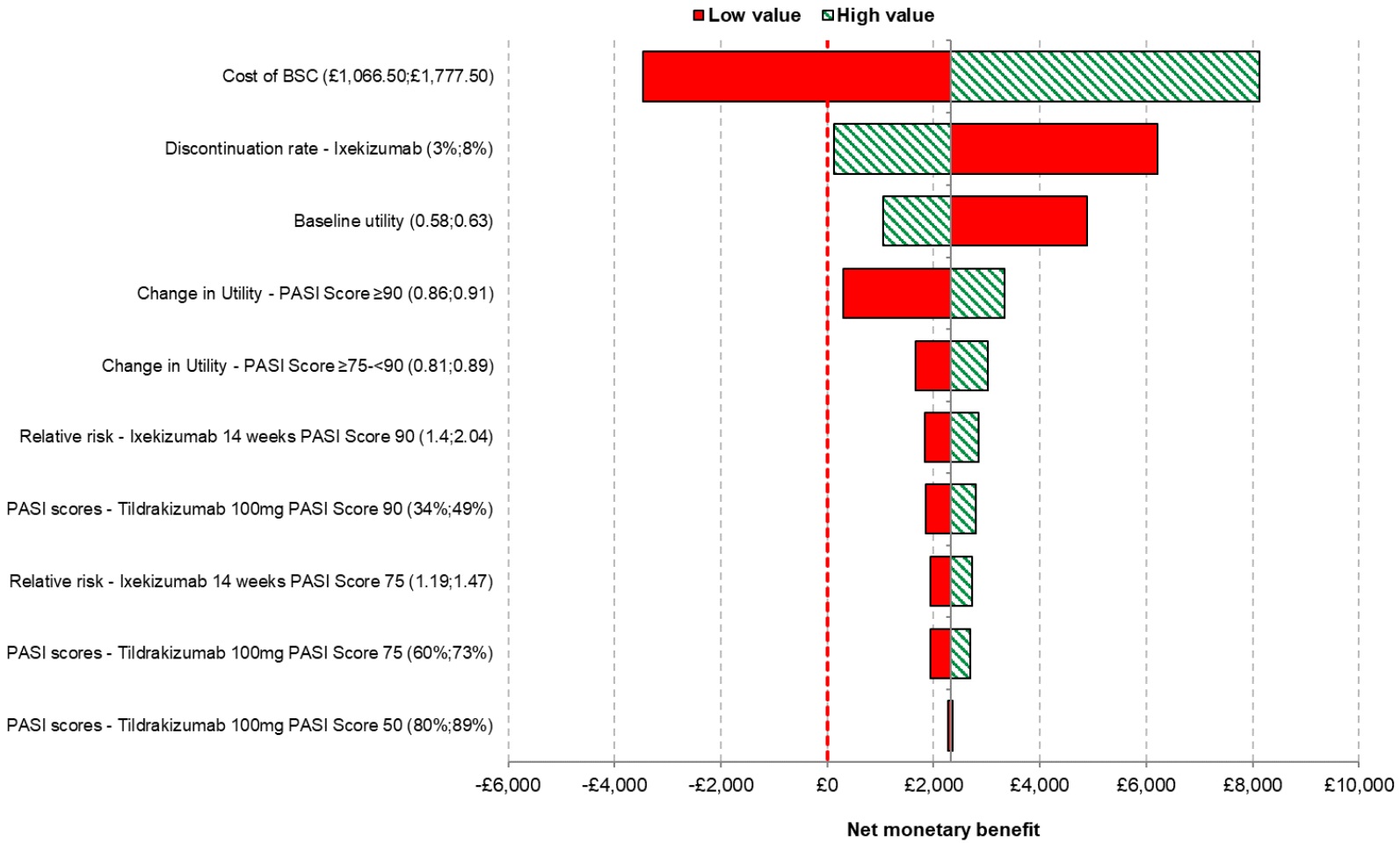
Guselkumab ([redacted] PAS)



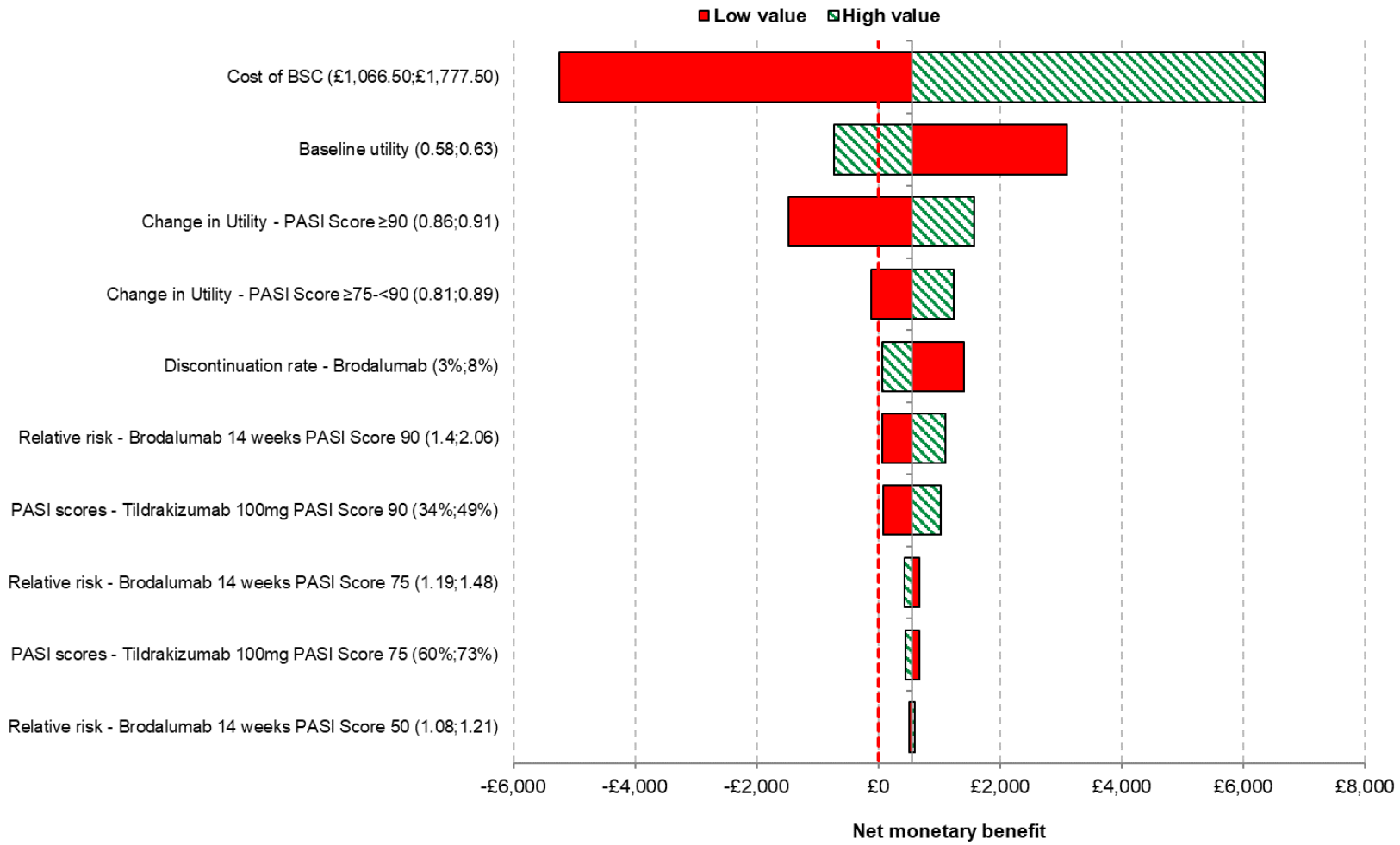
Secukinumab ([redacted] PAS)



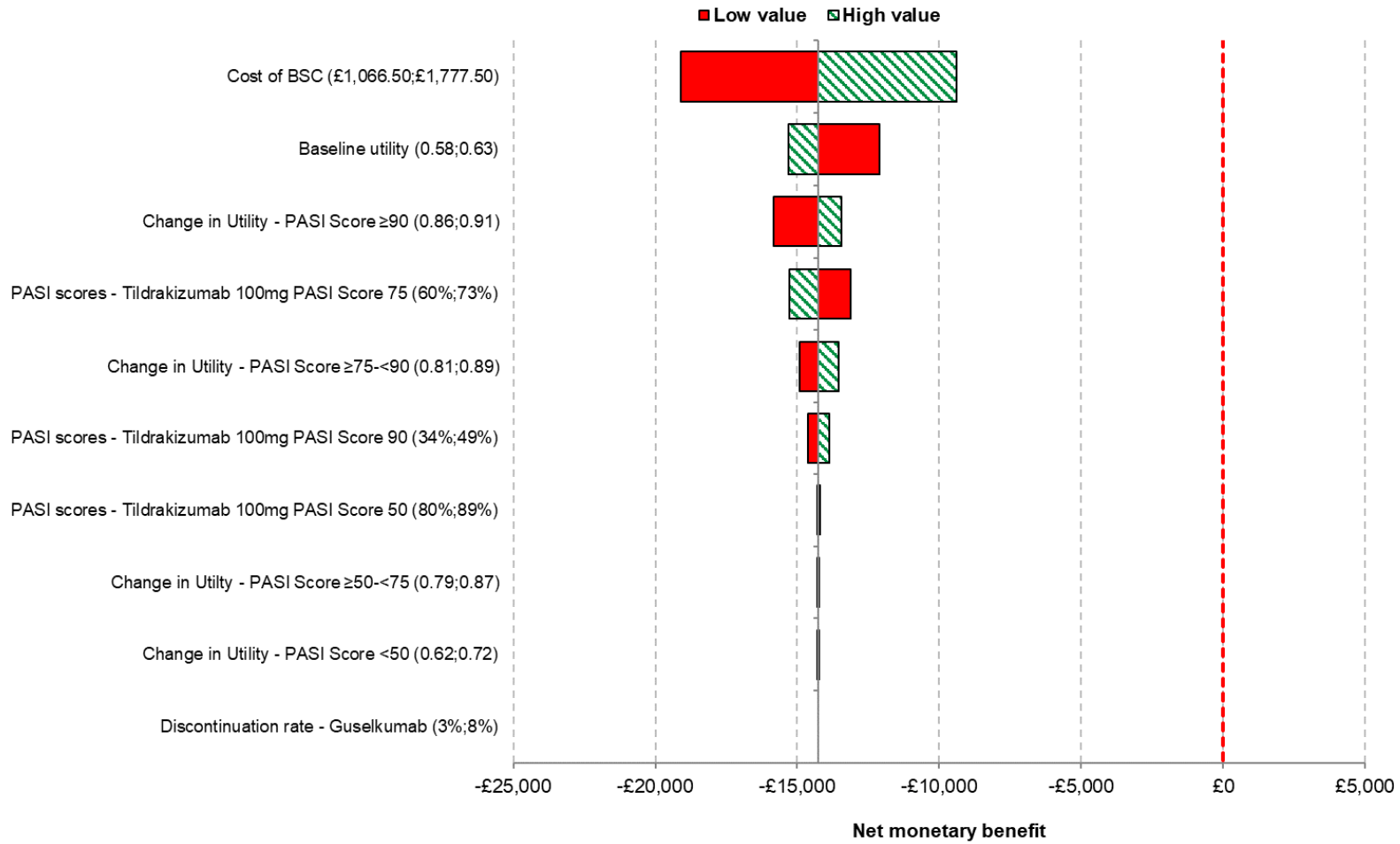
Ixekizumab ([redacted] PAS)



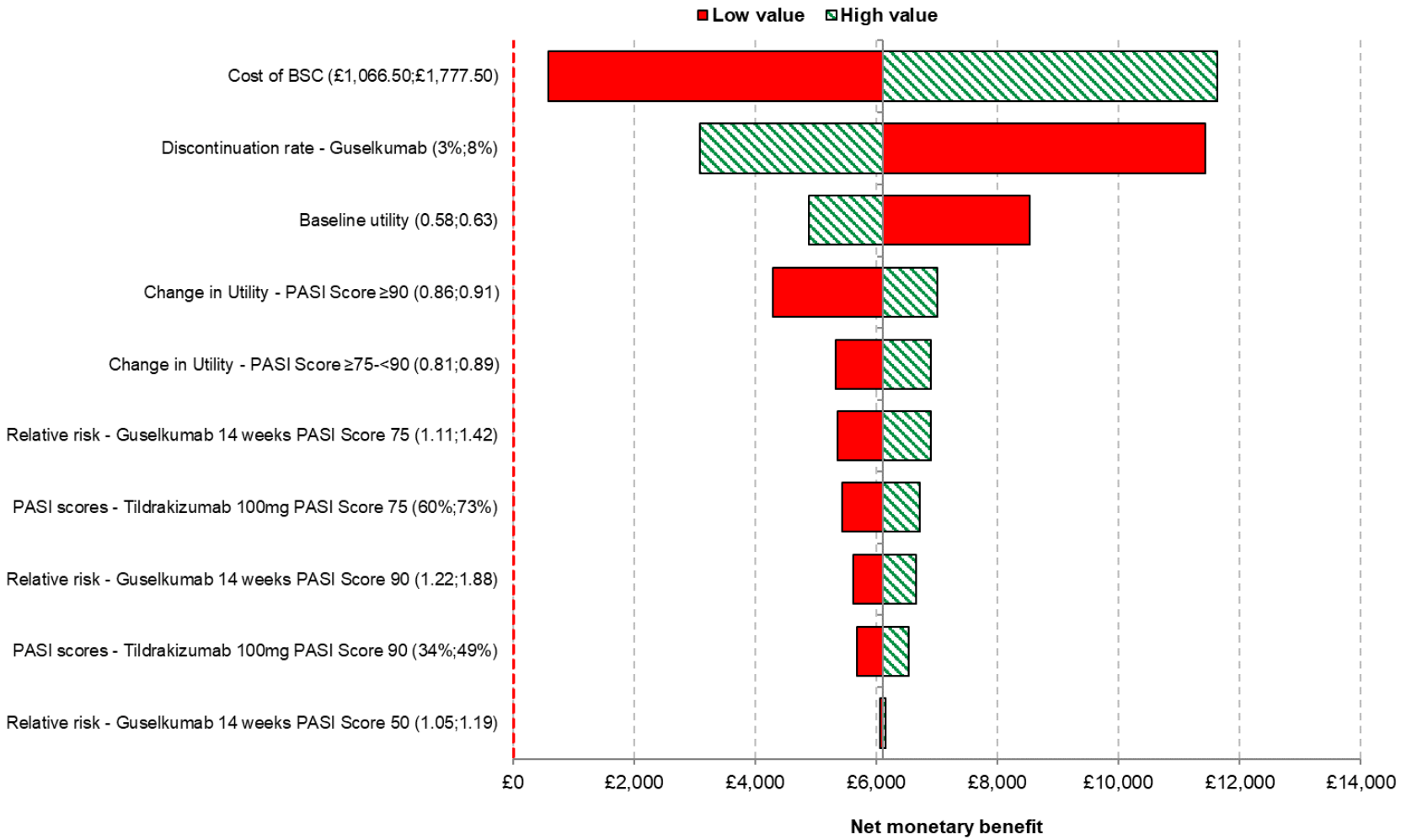
Brodalumab ([redacted] PAS)



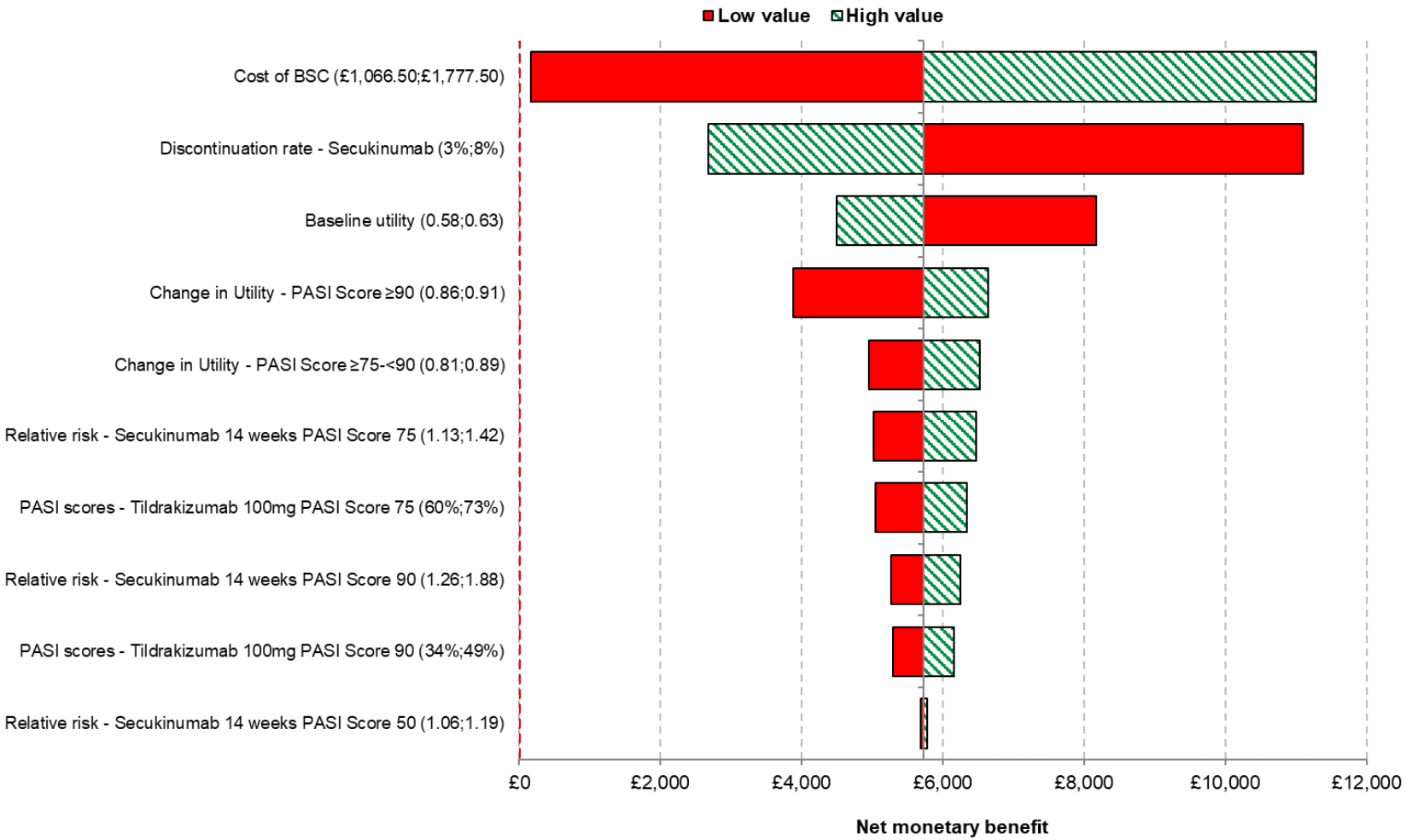
Infliximab (no PAS)



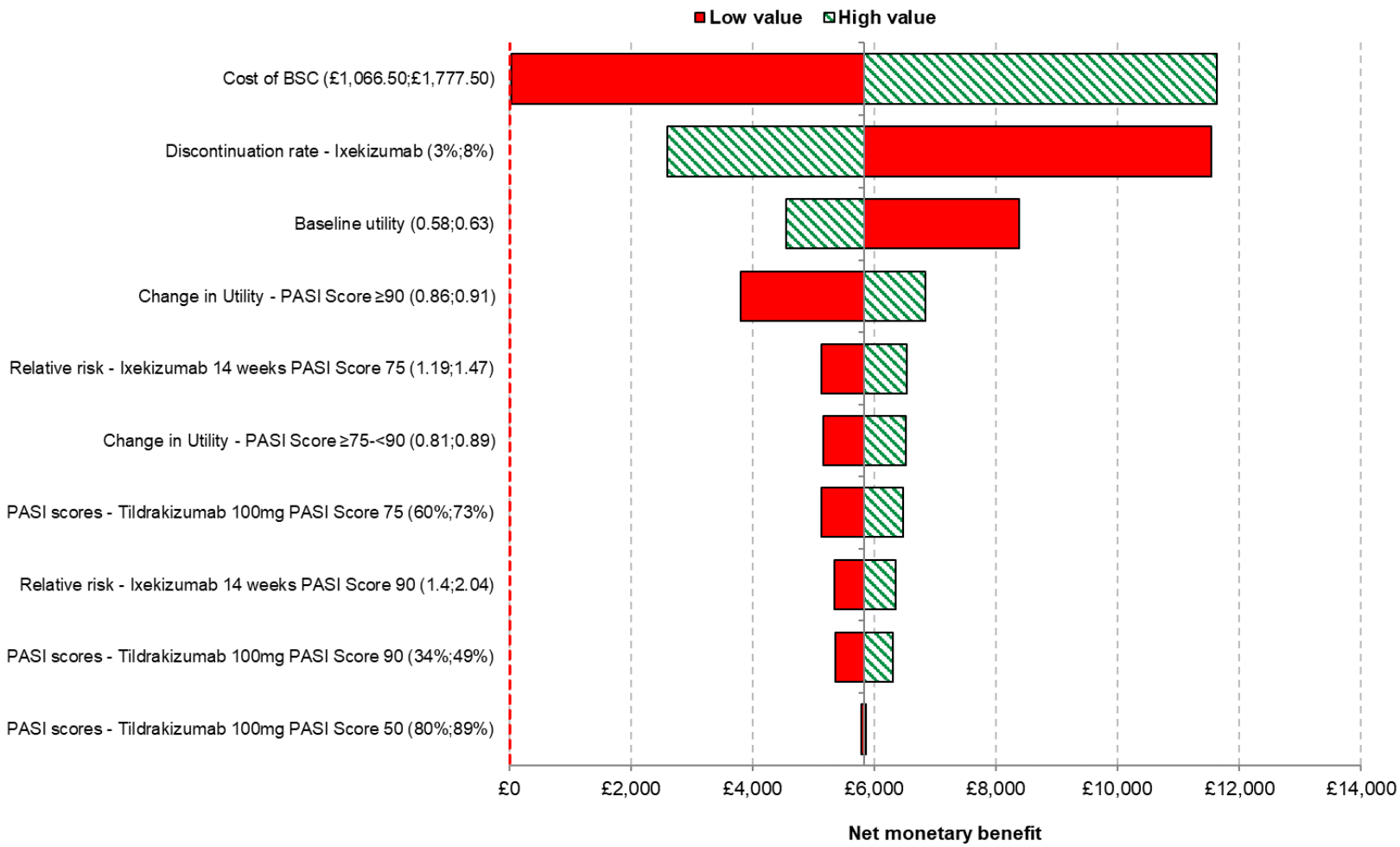
Guselkumab ([redacted] PAS)



Secukinumab ([redacted] PAS)



Ixekizumab ([redacted] PAS)



Brodalumab ([redacted] PAS)

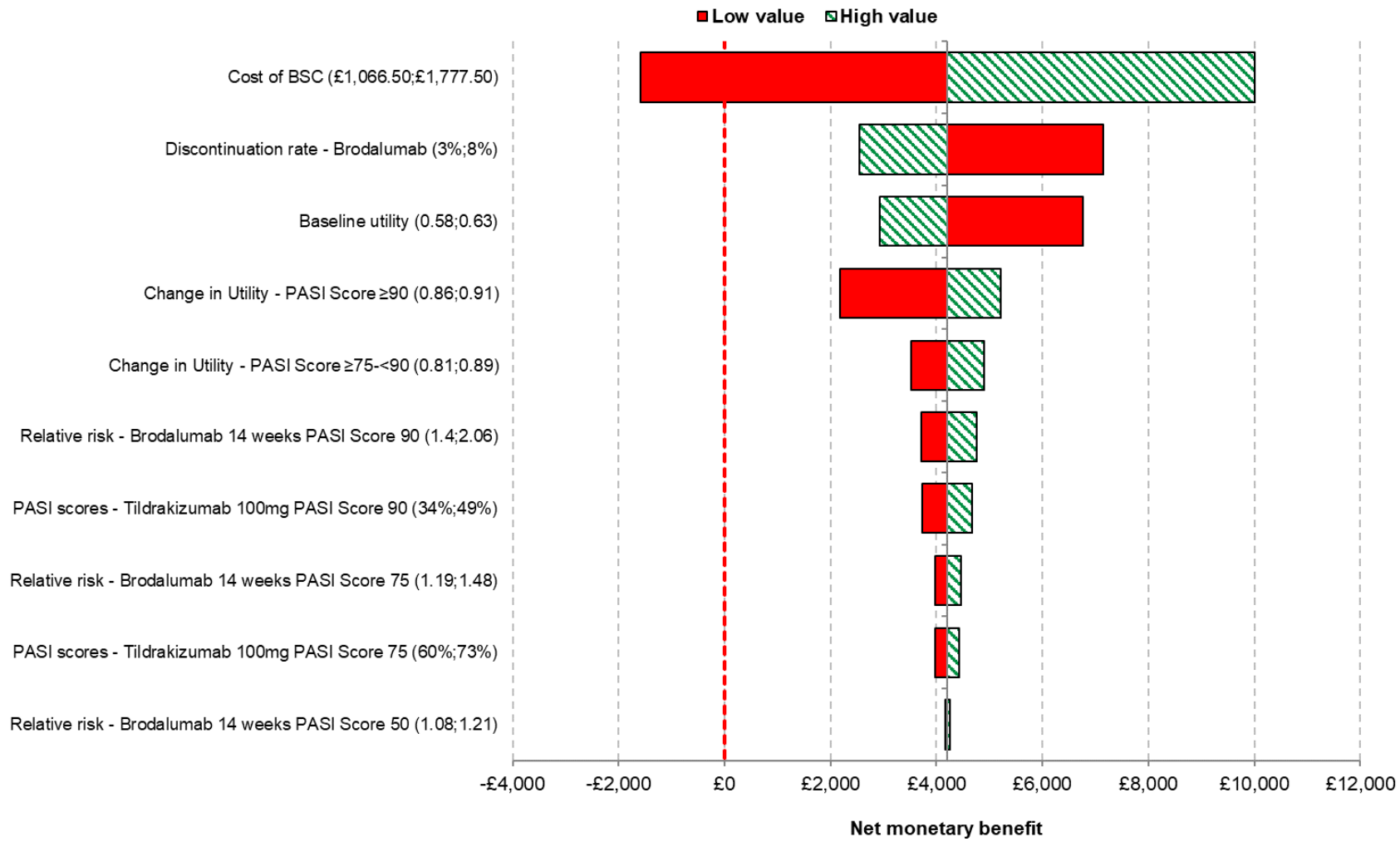
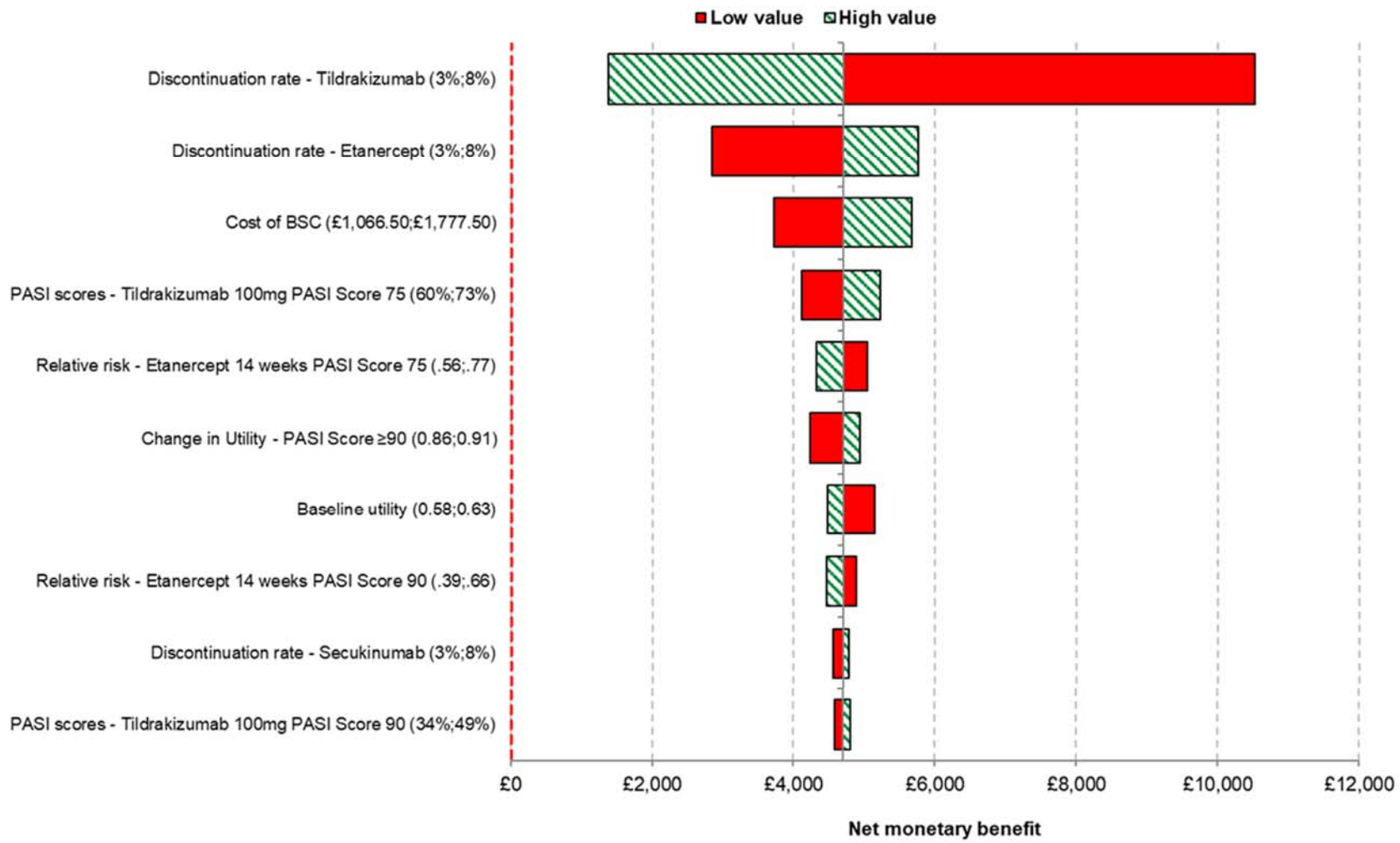
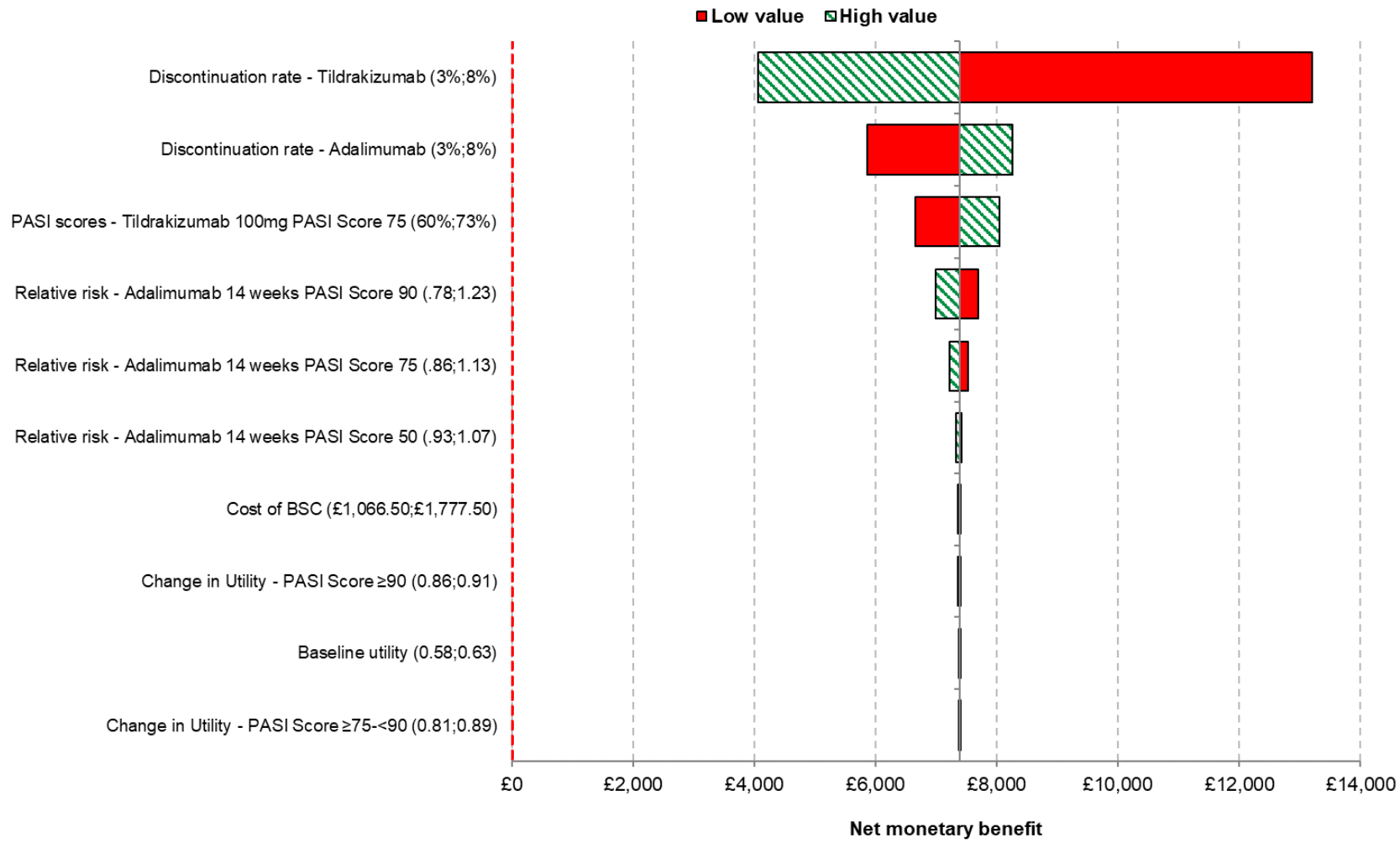


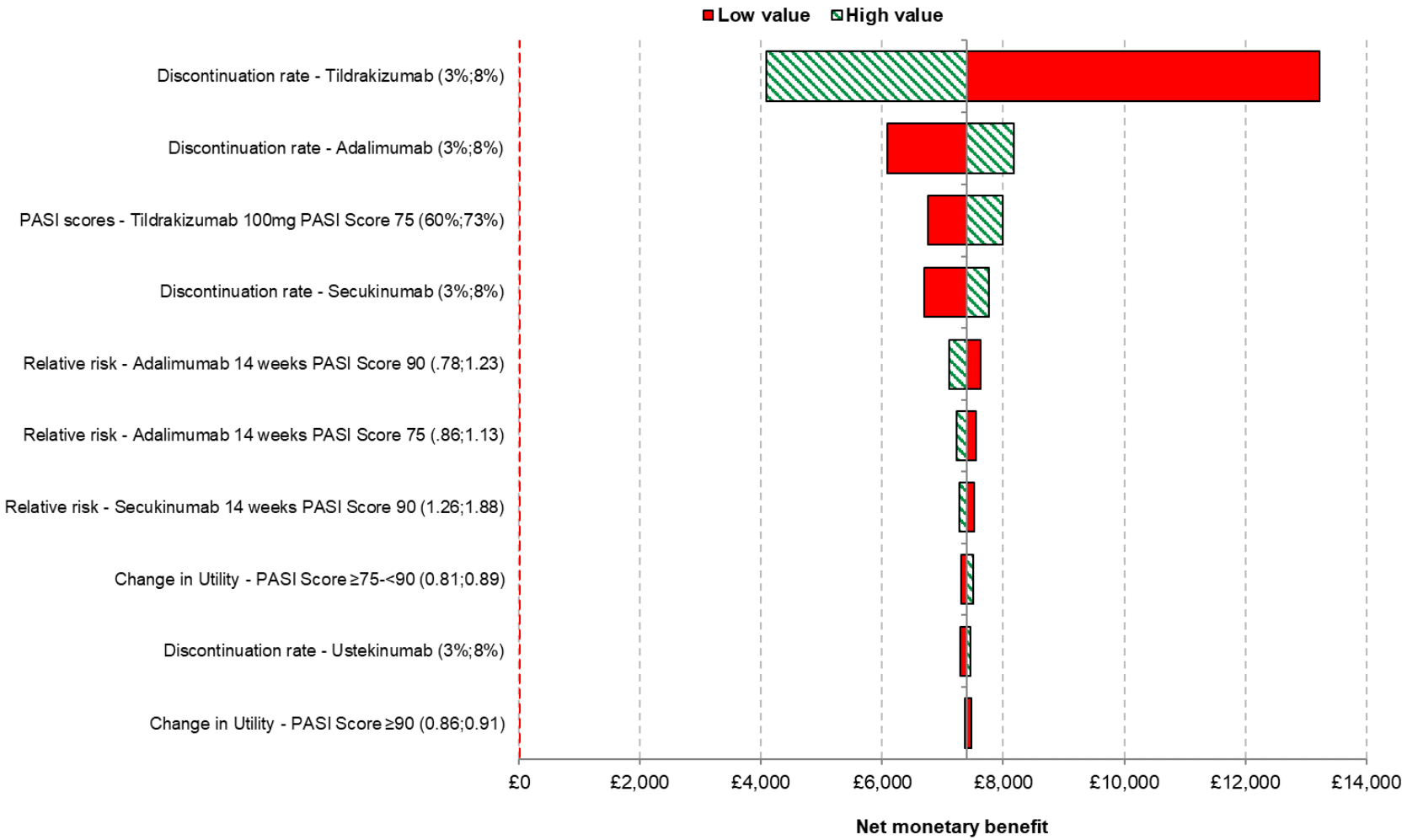
Figure B2 – tildrakizumab sequence (100mg, 14-weeks) versus all other sequences, [redacted] PAS Sequence 2 (Etanercept)



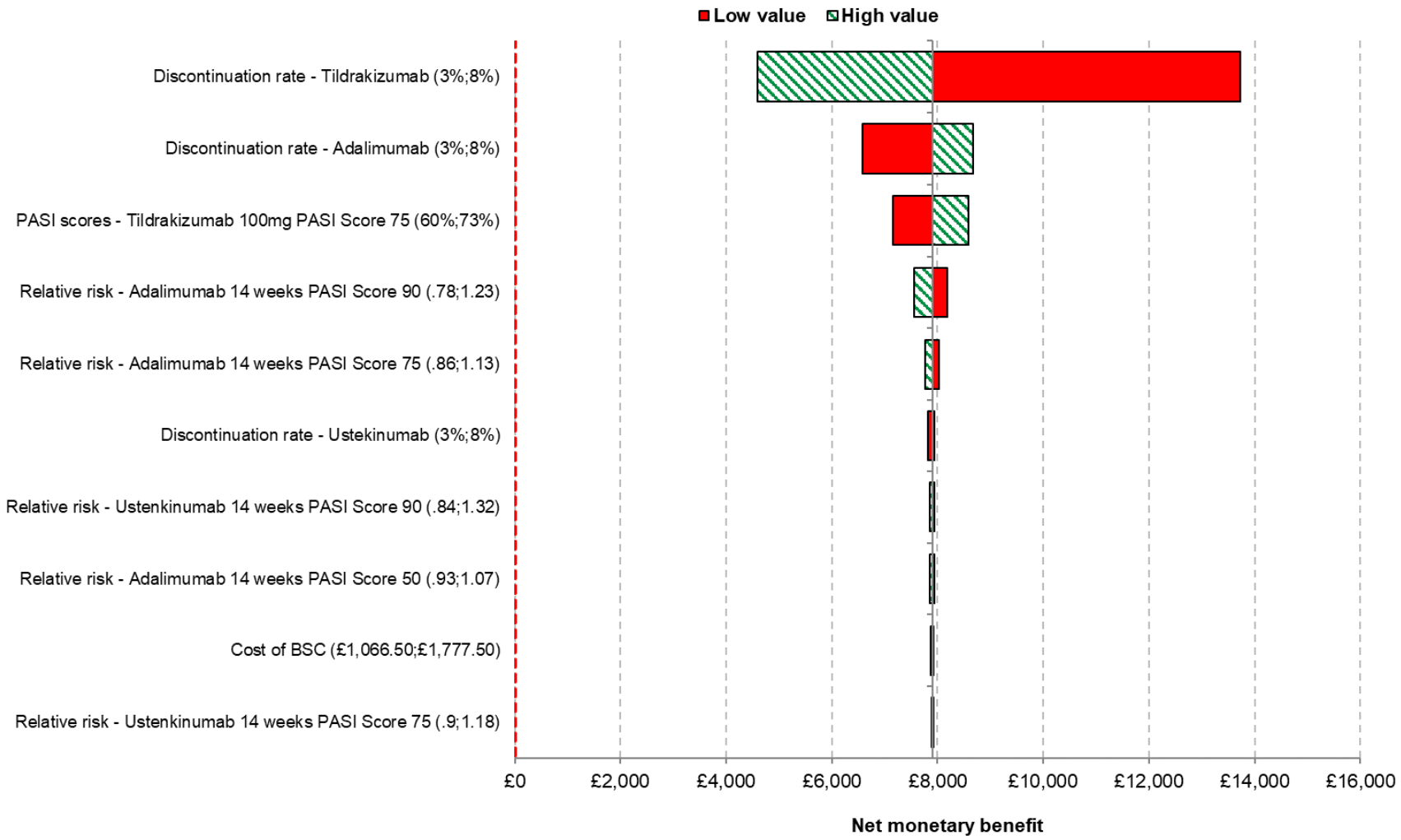
Sequence 4 (Adalimumab)



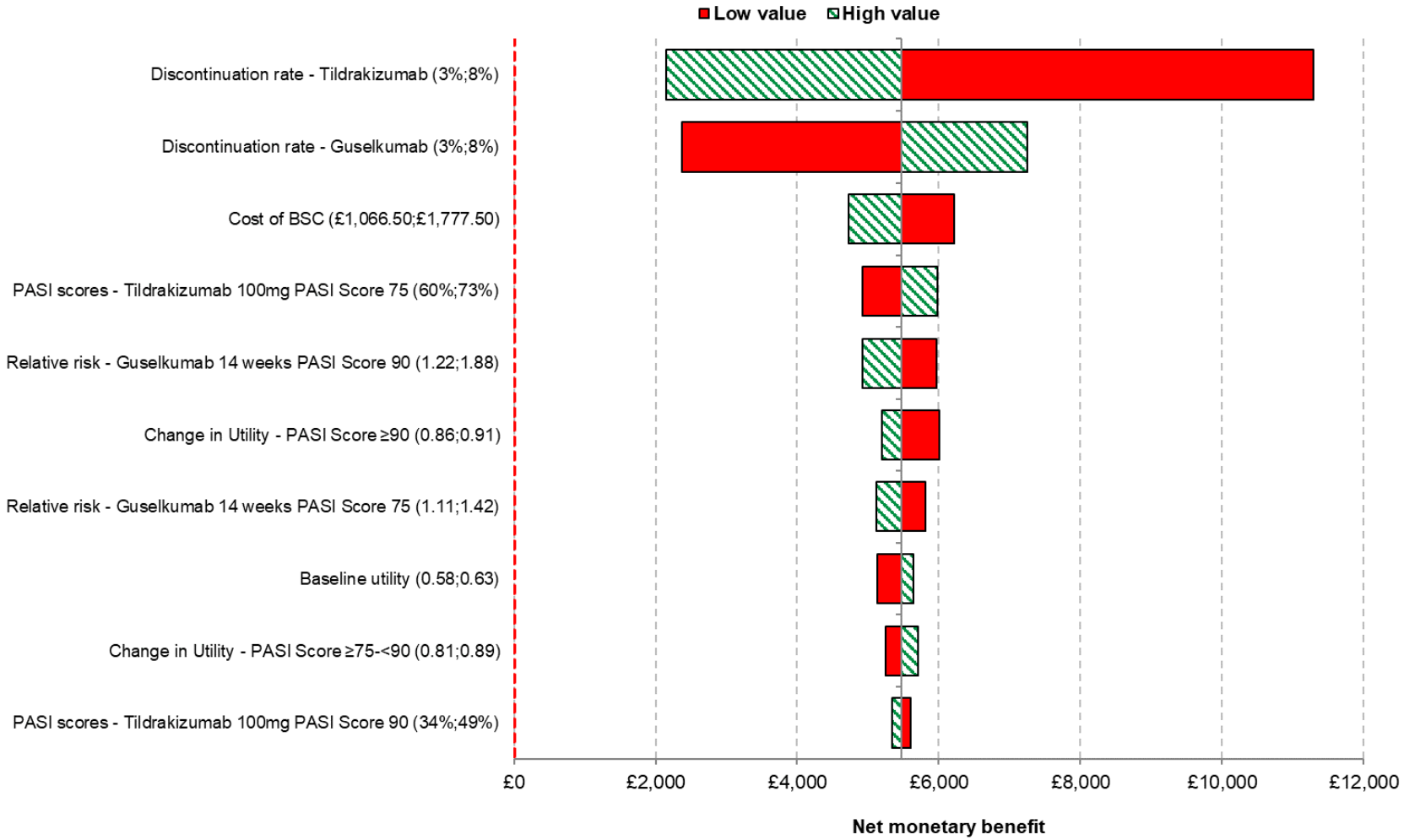
Sequence 5 (Secukinumab)



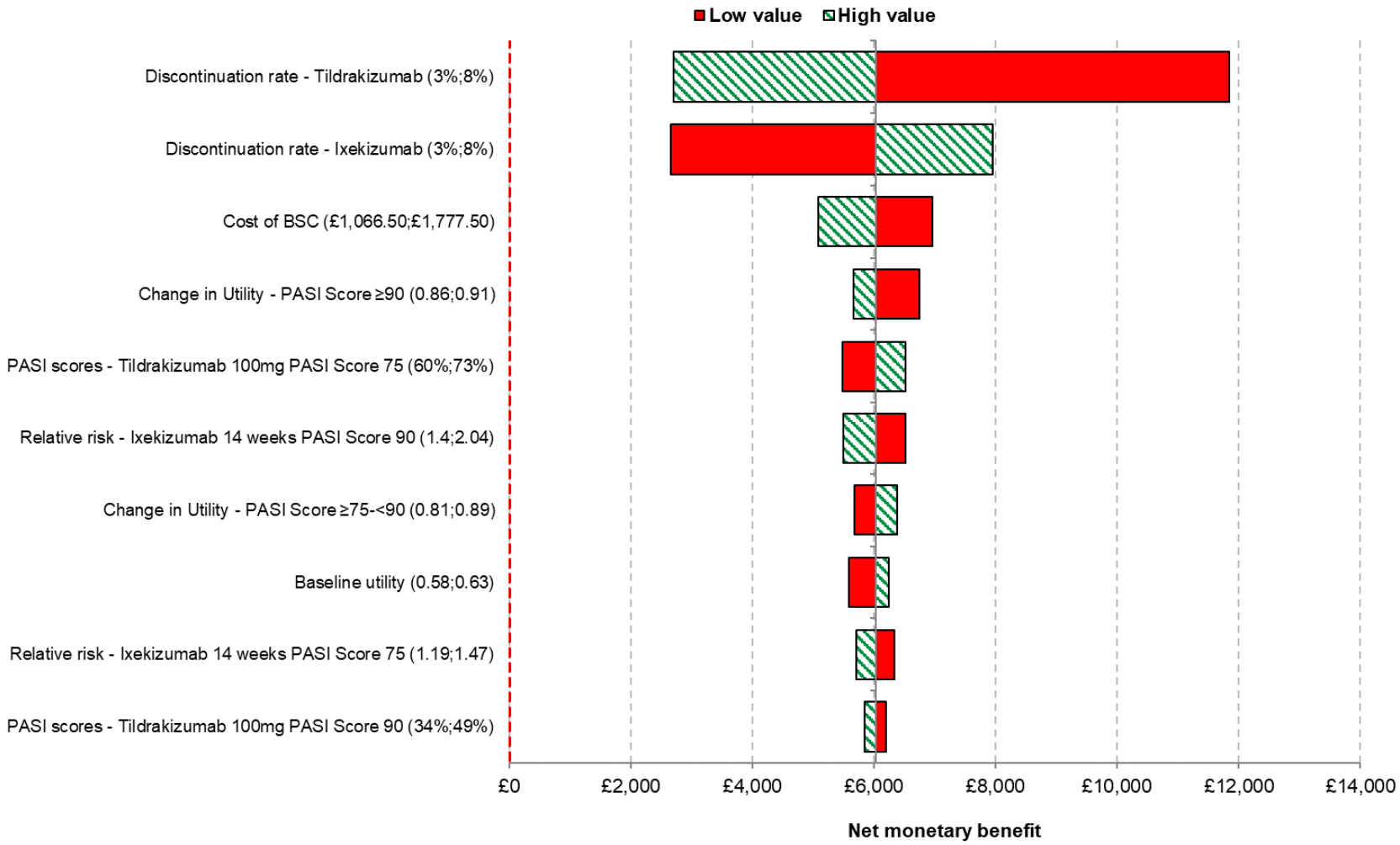
Sequence 6 (Ustekinumab)



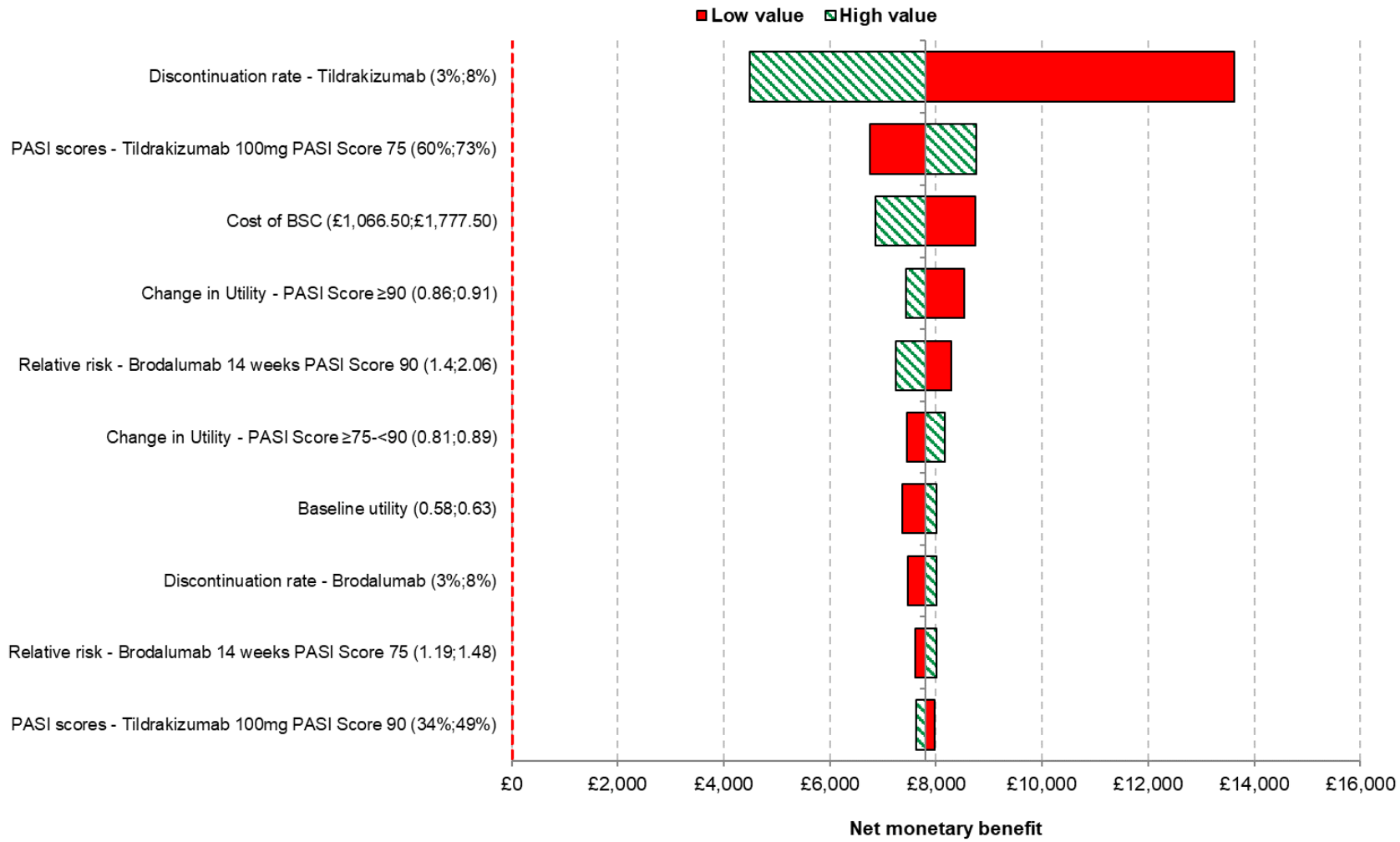
Sequence 7 (Guselkumab)



Sequence 8 (Ixekizumab)



Sequence 9 (Brodalumab)



Sequence 10 (Infliximab)

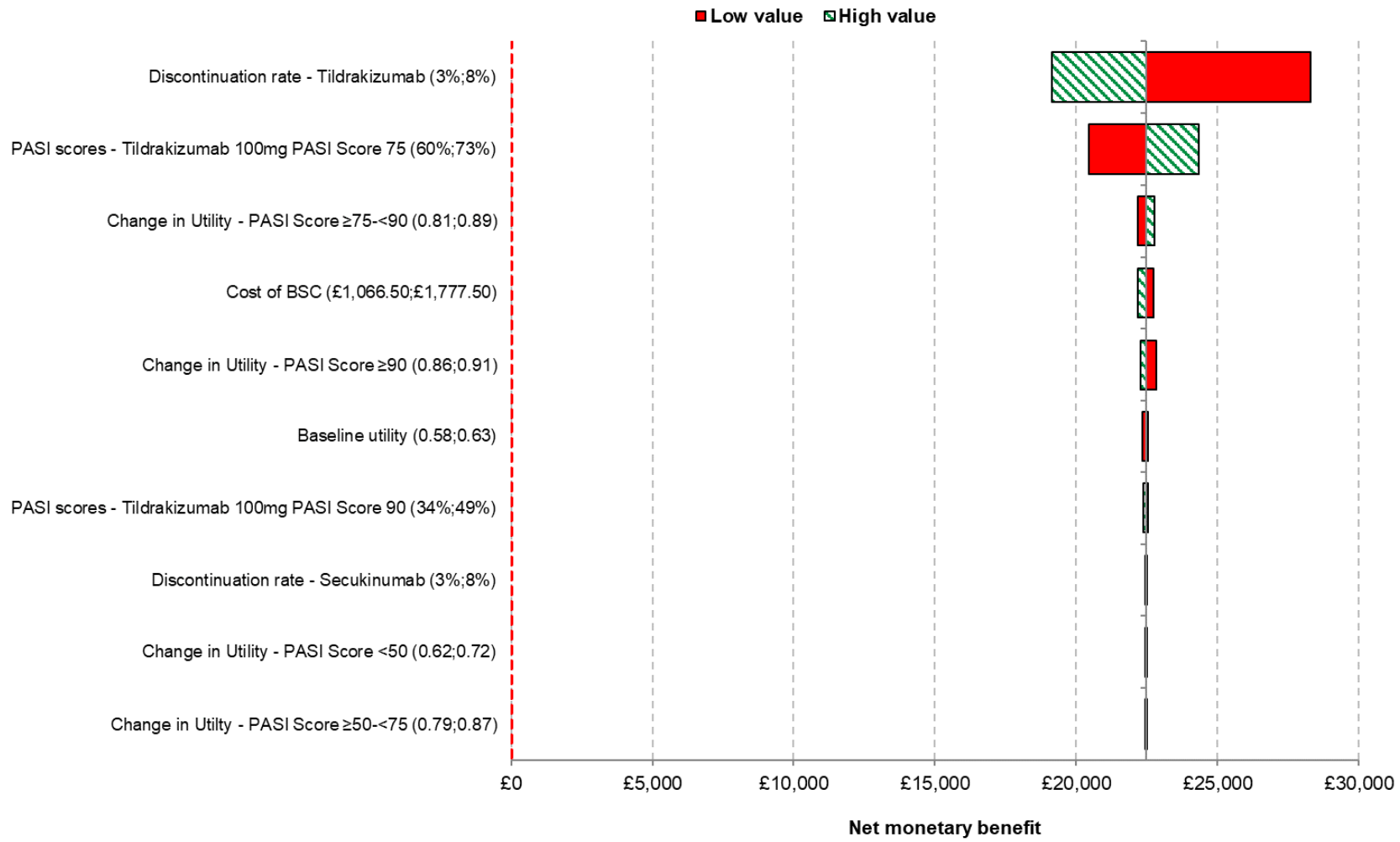
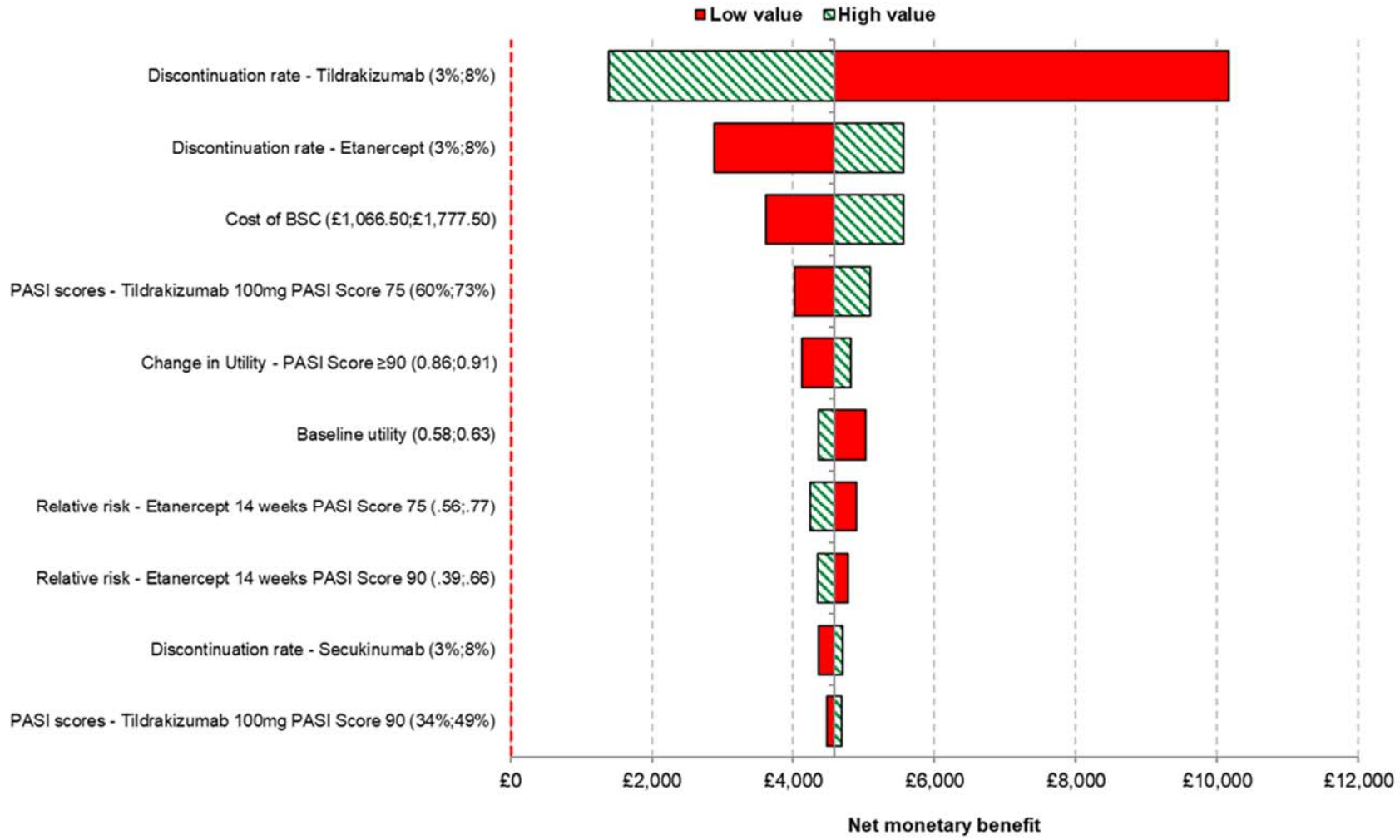
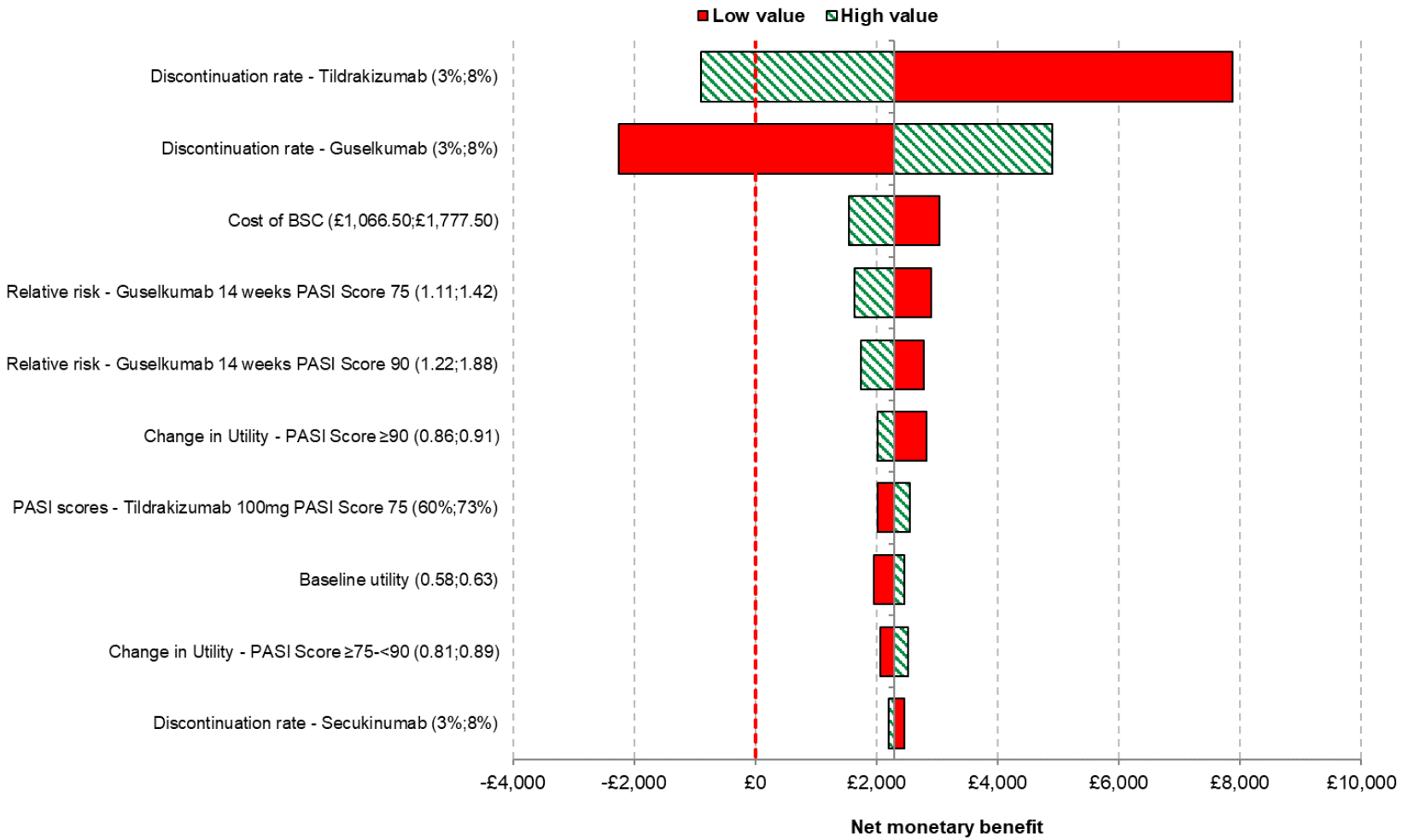


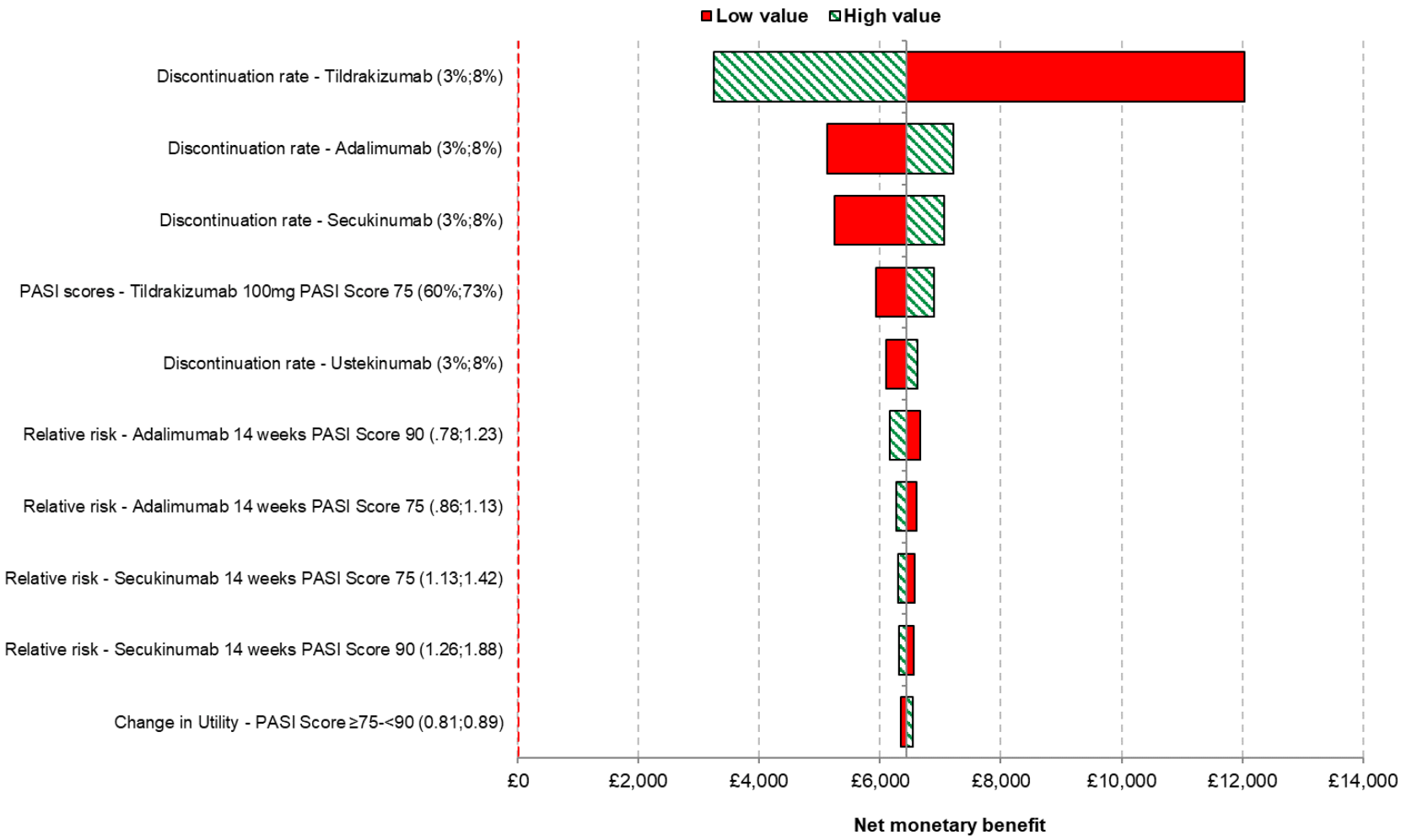
Figure B3 – tildrakizumab sequence (100mg, 14-weeks) versus all comparator sequences, [redacted] PAS Sequence 2 (Etanercept)



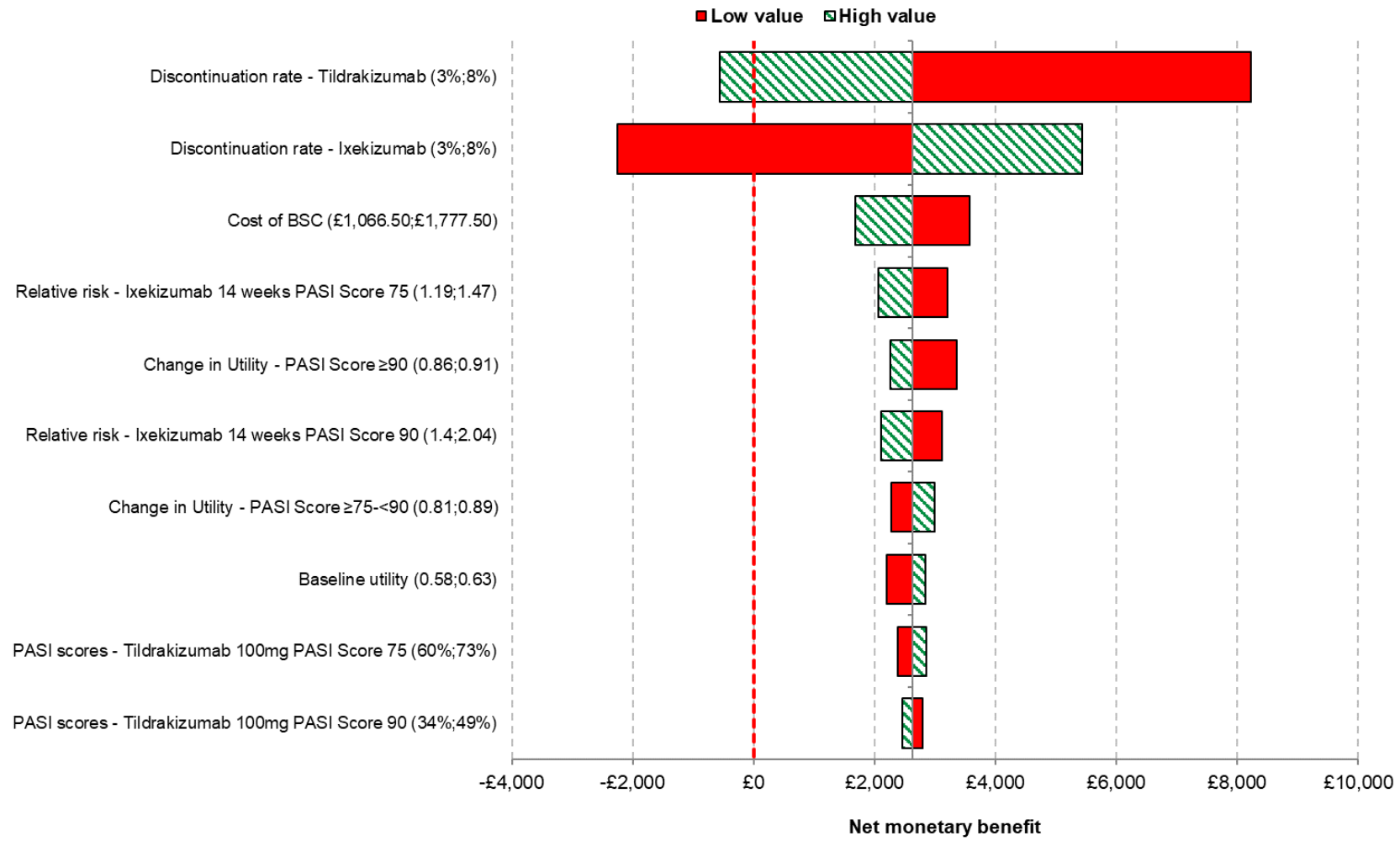
Sequence 7 (Guselkumab)



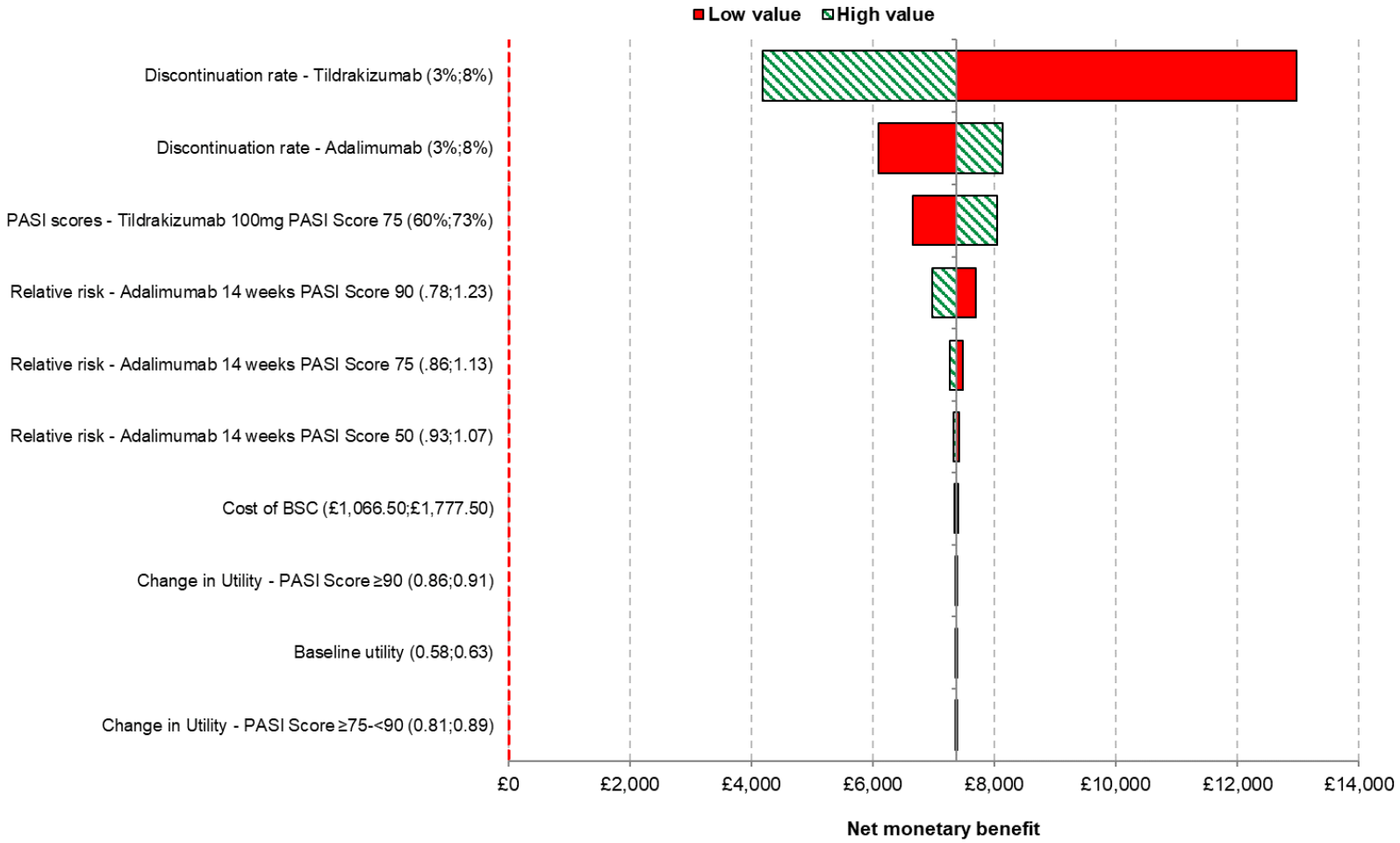
Sequence 5 (Secukinumab)



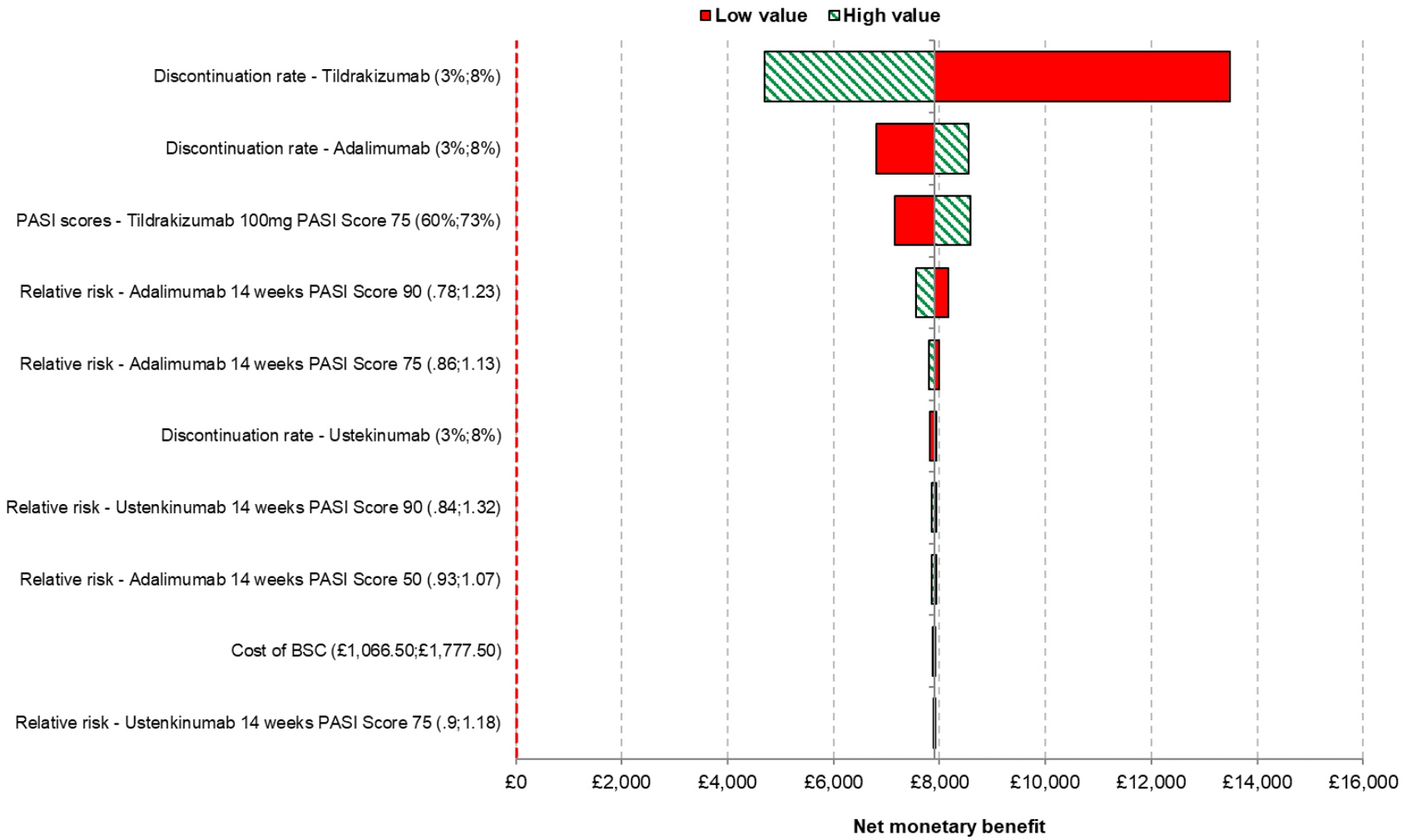
Sequence 8 (Ixekizumab)



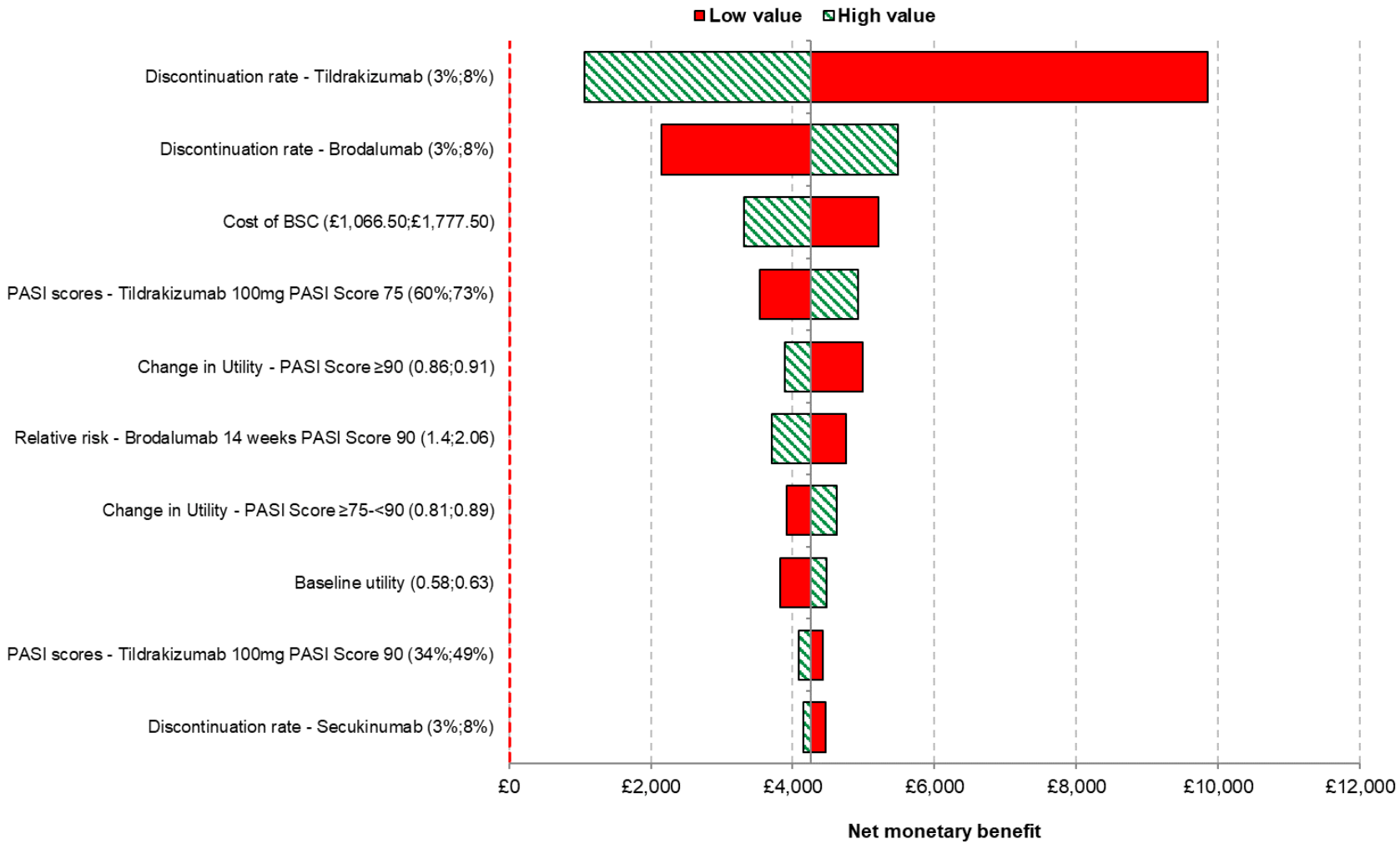
Sequence 4 (Adalimumab)



Sequence 6 (Ustekinumab)



Sequence 9 (Brodalumab)



Sequence 10 (Infliximab)