Single Technology Appraisal

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Novartis**

2. **Comments on the Draft Guidance from experts:**
   a. Ruth Lamb, Consultant Dermatologist – clinical expert, nominated by Novartis

3. **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance**

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

NICE National Institute for Health and Care Excellence

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 20 July 2023. Please submit via 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):	**Novartis Pharmaceuticals UK Ltd**

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not Applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Since April 2005 Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are composed of, or contain glycopyrronium bromide: • Seebri® Breezhaler® (glycopyrronium bromide) (used as a maintenance treatment for chronic obstructive pulmonary disease [COPD]) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with long-acting beta-agonist (LABA)/ inhaled corticosteroid (ICS) Phillip Morris International (a tobacco company) has acquired Vectura Group Limited (formerly Vectura Group plc).
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.
1	**Executive summary** Novartis thanks NICE for the opportunity to comment on the Draft Guidance Document (DGD) and welcomes the appraisal Committee's conclusion that: • Moderate to severe hidradenitis suppurativa (HS) has a substantial burden on quality of life, and alternatives to surgery and existing biological treatment are needed • The treatment pathway presented by the Company, based on the guidelines of the British Association of Dermatologists, broadly reflects treatments given in NHS practice • The Company's positioning of secukinumab in the treatment pathway was appropriate • It was plausible that secukinumab improved outcomes compared with placebo • The results of the full trial population, including people who had previous biologics and those who did not, were generalisable to the Company's narrower target population of people with moderate to severe HS who cannot take adalimumab, including those for whom adalimumab did not work or stopped working • The Company's hospital resource use rates were appropriate for use in the model Novartis is, however, disappointed with the draft guidance to not recommend secukinumab for the treatment of patients with moderate to severe HS who cannot have adalimumab or whose condition has not responded to adalimumab, considering that "*the Committee concluded that moderate to severe HS has a substantial burden on quality of life, and alternatives to surgery and existing biological treatment are needed*" (Section 3.2 of the DGD). Currently, other than adalimumab, secukinumab is the only licensed and effective biologic treatment with a tolerable safety profile available for patients with active moderate to severe HS, which has the potential to address a considerable unmet medical need. Novartis remains committed to working with NICE to secure a positive outcome, enabling patient access to secukinumab for treating moderate to severe HS. To support the case for the positive recommendation of secukinumab in the anticipated positioning, Novartis would like to focus the response on the key areas of uncertainty raised in the DGD. These include: • A scenario where people who have no response in the maintenance phase of the model stop secukinumab and instead have best supportive care (BSC) in line with technology appraisal guidance TA392 (section 3.11 of the DGD) • Further validation of the model output with clinical expert input and comparison with additional sources of evidence to support the choice of the best source of data (section 3.12 of the DGD) • A scenario in which a declining proportion of people in the response state of the BSC arm is modelled over time (section 3.12 of the DGD) • A model that reflects the responses seen in the SUNNY trials at Week 16 in the secukinumab and placebo arms (section 3.13 of the DGD) • Additional data to support the use of treatment-specific utility beyond Week 16 (section 3.14 of the DGD)

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Furthermore, while Novartis acknowledges the current Committee-preferred assumption to not include up-titration in the model as this was not evaluated in the SUNNY trials, results in this response are presented with and without up-titration for transparency and completeness. As discussed in DGD Response Comment 4, this is because (1) the possibility of up-titration is part of the licence for secukinumab and is therefore likely to reflect clinical practice, (2) while similar efficacy results were reported for the every 4 weeks (Q4W) and every 2 weeks (Q2W) dosing regimens, some patients may benefit from up-titration, and (3) the possibility to up-titrate is clinically important to patients and clinicians considering the absence of alternative treatment options.

As part of this response, Novartis has made amendments to the base-case presented during Technical Engagement (TE) to reflect the Committee discussion and preferred assumptions on some of the uncertainties raised in the DGD. Other aspects of the analysis continue to use earlier assumptions and are supported by additional data. The revised Novartis base-case following DGD includes the following:

Committee-preferred assumptions

1. Alignment of treatment costs with those used in the SUNNY trials (see DGD Response Comment 3).
2. Inclusion of a scenario removing up-titration (see DGD Response Comment 5); As mentioned, however, a scenario including up-titration is also presented for transparency and completeness and remains the company-preferred approach.
3. Inclusion of a stopping rule (see DGD Response Comment 6).
4. Use of per 4-week cycle transition probabilities for the Induction phase of the model (see DGD Response Comment 7).

Original assumptions (i.e., no revisions made) supported by additional data

1. Using the transition probabilities for the BSC arm derived from the PIONEER II trial (NICE TA392) beyond Week 16 (see DGD Response Comment 8).
2. Using treatment-specific utility values for the non-responder health state beyond Week 16 (see DGD Response Comment 9).
3. Using a Committee-preferred approach in TA392 to model surgery costs (see DGD Response Comment 10).
4. Using the number of outpatient visits as reported in the survey in TA392 (see DGD Response Comment 11).

Results presented in this response use the patient access scheme (PAS) simple discount agreed in TA350 (secukinumab for treating moderate to severe plaque psoriasis) in line with the NICE methods guide.[1, 2] [redacted]

The revised Novartis base-case (probabilistic) following DGD is presented, including up-titration (Table 1 – company-preferred approach) and excluding up-titration (Table 2).

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Table 1: ICERs for the Company's revised base-case following DGD (probabilistic), including up-titration (Company-preferred approach).

Treatment	Costs	Lys	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Base-case submitted at TE							
BSC	[redacted]	22.724	[redacted]	-	-	-	-
SEC	[redacted]	22.724	[redacted]	[redacted]	0.000	[redacted]	£42,439
Revised base-case following DGD							
BSC	[redacted]	22.699	[redacted]	-	-	-	-
SEC	[redacted]	22.699	[redacted]	[redacted]	0.000	[redacted]	£54,070

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab; TE, technical engagement.

Table 2: ICERs for the Company's revised base-case following DGD (probabilistic), excluding up-titration.

Treatment	Costs	Lys	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Base-case submitted at TE							
BSC	[redacted]	22.729	[redacted]	-	-	-	-
SEC	[redacted]	22.729	[redacted]	[redacted]	0.000	[redacted]	£43,443
Revised base-case following DGD							
BSC	[redacted]	22.752	[redacted]	-	-	-	-
SEC	[redacted]	22.752	[redacted]	[redacted]	0.000	[redacted]	£60,898

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab; TE, technical engagement.

2

Clinical validation

In response to the DGD, further clinical validation was sought to validate inputs, assumptions, and plausibility of model results. A total of seven clinical experts were consulted.[3]

- Three clinical experts during a 2-hour face-to-face advisory board (Ad Board) held on Thursday 29 June 2023.
- Four clinical experts during 1-hour virtual individual consultations (held Friday 30 June – 5 July 2023).

A mixture of face-to-face and virtual individual consultations were conducted due to the challenge in finding a suitable time for all participants. Pre-reading material was shared before the Ad Board/individual consultations and consisted of the DGD.

The focus of discussion was the key issues raised in the DGD, and included:

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	1. Clinical plausibility of prediction and best source of evidence to use to inform the BSC transition beyond Week 16 (see DGD Response Comment 8), 2. Source of evidence about the effectiveness of current treatments that are part of BSC (see DGD Response Comment 3), 3. Stopping rule for secukinumab (see DGD Response Comment 6), 4. Clinician view of up-titration (see DGD Response Comment 5). As time permitted, the following topics were also covered: 5. Use of treatment-specific utility values (see DGD Response Comment 9), 6. Number of outpatient visits expected (see DGD Response Comment 11). Ad Board slides, Ad Board report, and a summary of the individual consultations are provided as part of this response for transparency and completeness. In addition to the Ad Board and individual consultations, a follow-up email was sent to all participants (on 10 July) to help determine the most appropriate approach to cost of surgery. Clinical inputs for the different topics are summarised in the relevant sections of the response below when appropriate.
3	**Alignment of BSC treatment costs with treatments used in the SUNNY trials (DGD Section 3.15)** Novartis acknowledges the Committee's concerns regarding the potential misalignment of the BSC arm of the SUNNY trials with NHS clinical practice. The Committee noted that individuals receiving BSC treatments permitted in the SUNNY trials may have worse efficacy outcomes compared to those receiving BSC in clinical practice, and thus including only the costs of these treatments within the model may bias results in favour of secukinumab. The Committee considered that, without data on response to treatments given in UK clinical practice, it preferred to align the costs of BSC in the model with the placebo arm of the SUNNY trials. Clinical experts were consulted to identify potential sources of evidence that could be used to determine the response according to different treatments that are part of BSC (see DGD Response Comment 2).[3] Consistent with the clinical expert statement during the Appraisal Committee Meeting (ACM) (Section 3.12 of the DGD), all clinical experts consulted noted that there is a lack of effectiveness data for treatment given in UK practice and they were not aware of any data that could be used to validate this assumption.[3] Clinical experts noted that the efficacy for conventional treatments may depend on patient phenotype.[3] They further indicated that comparing the efficacy of oral antibiotics with other treatments is difficult as there are no trials to guide this and that it would be based on individual clinical judgement which is not robust evidence.[3] While recognising the absence of data, Novartis would like to highlight that most patients with moderate to severe HS require biologic treatment due to disease progression resulting from inadequate response to components of BSC. Furthermore, despite the limited evidence, clinicians often opt to retry these treatments with the hope of achieving some response in their patients before considering surgical interventions. Nevertheless, Novartis recognises the uncertainty and absence of data and revised its base-case accordingly to align costs with BSC treatments in the SUNNY trials to reflect the Committee-

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<table>
<tr><td></td><td>preferred assumptions (see Table 1 and Table 2). This approach also aligns with that used in TA392.</td></tr>
<tr><td>4</td><td>Long-term efficacy (DGD Section 3.8)
Novartis acknowledges the Committee's concerns regarding the lack of long-term clinical effectiveness data for secukinumab in the SUNNY trials. While Novartis understands the importance of robust evidence to support the evaluation of cost-effectiveness, Novartis would like to emphasise that clinical experts highlighted a noteworthy finding that “response rates increased by around 5% to 25% between Week 16 and Week 52 across treatment arms and doses” (Section 3.8 of DGD). Indeed, as shown in Table 3, pooled SUNNY trials data indicate that almost 80% of the responders (defined as HiSCR≥50) at Week 16 maintained response up to Week 52, and almost half of the non-responders (defined as HiSCR<50) at Week 16 gained a response at Week 52.

Table 3: Shift table for HiSCR50 response rates from Week 16 to Week 52 using observed pooled SUNNY trials data (Full Analysis Set)
<table>
<tr><th rowspan="2">Treatment</th><th colspan="2">Week 16</th><th colspan="2">Week 52</th></tr>
<tr><th></th><th>n (%)</th><th>Response
n (%)</th><th>No response
n (%)</th></tr>
<tr><td rowspan="3">SEC Q4W</td><td>Response</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>No response</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Total</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td rowspan="3">SEC Q2W</td><td>Response</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>No response</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Total</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: HiSCR: hidradenitis suppurativa clinical response; Q2W: every 2 weeks; Q4W: every 4 weeks; SEC: secukinumab.

Novartis believes that these findings are not only encouraging, but also strongly suggest the potential for secukinumab to deliver sustained long-term effectiveness in improving outcomes for patients with active moderate to severe HS: an area acknowledged by the Committee as facing a considerable unmet need for other licensed and effective biologic treatments. Furthermore, the results demonstrate that some patients who initially did not respond to secukinumab (defined as HiSCR<50) may still have a chance of responding positively if they continue treatment with secukinumab.

In conclusion, the results from the SUNNY trials demonstrate that secukinumab is effective at both maintaining response in initial responders and potentially eliciting a response in Week 16 non-responders (defined as HiSCR<50) over a longer treatment period. Therefore, using secukinumab in HS at its anticipated positioning would represent a step-change in the treatment of patients in this line of therapy, where there is a lack of robust, licensed and evidenced-based treatments for HS.</td></tr>
<tr><td>5</td><td>Up-titration (DGD Section 3.10)
While Novartis acknowledges the concerns raised by the External Assessment Group (EAG) and the Committee regarding the modelling of up-titration in the original Company submitted model and following TE and thus their preference to exclude up-titration, the inclusion of up-titration remains the company-preferred approach. This is because:</td></tr>
</table>

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	1) The possibility of up-titration is part of the licence for secukinumab and is therefore likely to reflect clinical practice; 2) While similar efficacy results were reported for every 4 weeks (Q4W) and every 2 weeks (Q2W) dosing regimens in the SUNNY trials, some patients may benefit from up-titration; and 3) The possibility to up-titrate is clinically important to patients and clinicians considering the absence of alternative treatment options. To support Points 1 and 3 above, the clinical experts consulted during the ACM emphasised the importance of dose adjustment from Q4W to Q2W for improved dose response. Additionally, "*the Committee considered that it may be appropriate to use up-titration in clinical practice*" (Section 3.10 of the DGD). To further support these insights from the ACM, clinical experts consulted by Novartis (see DGD Response Comment 2) were asked to further comment on the importance of the NICE recommendation to include up-titration. All clinical experts felt that allowing the flexibility to customise the dose based on clinical response in line with the licensed posology is important as some patients may benefit from being up-titrated, as per the clinical experience of the experts in plaque psoriasis and the absence of alternative treatment options following non-response to the secukinumab Q4W dosing regimen.[3] Regarding Point 2 above, a post hoc analysis of the SUNNY trials presented at the 12th European Hidradenitis Suppurativa Foundation e.V. (EHSF) Congress (P149; Florence, Italy; 8–10 February 2023) demonstrated that patients with more severe disease (greatest number of inflammatory nodules, abscesses and draining tunnels/fistulae) and the longest time since HS symptom onset (16.2 ± 10.6 years) benefited from more frequent dosing (secukinumab Q2W) as compared with less frequent dosing (secukinumab Q4W) up to Week 52.[4] Specifically, secukinumab Q2W achieved numerically greater benefits in terms of HiSCR50 (61.0% versus 56.9% for Q4W), abscesses and inflammatory nodule (AN) count (−57.6% versus −49.6% for Q4W), the proportion of patients experiencing HS flares (16.3% versus 37.5% for Q4W) and the proportion achieving NRS30/skin pain (58.0% versus 45.5% for Q4W).[4] For the above reasons, Novartis considers that it is important for the availability of the Q2W dosing regimen to be included in the model to reflect the licence for HS and the anticipated and preferred clinical use of secukinumab within the NHS. As such, the cost-effectiveness results are presented, including up-titration (Company-preferred approach) and excluding up-titration for transparency and completeness. This is for the Committee to have all information available to make an informed decision and ensure that the recommendation aligns with the licence for secukinumab in the HS indication and clinical needs for this HS population.
6	**Stopping secukinumab (DGD Section 3.11)** Novartis acknowledges the Committee's concerns regarding the discontinuation approach applied in the Company's model for the non-response health state during the Maintenance phase, which may not be in full alignment with NHS clinical practice. To address this concern, the Novartis revised base-case includes a stopping rule for secukinumab in line with the approach used in TA392 for stopping adalimumab. Clinical experts consulted during the face-to-face Ad Board and individual consultations (see DGD Response Comment 2) recommended the inclusion of a stopping rule at Week 16 if patients did not respond in a scenario where up-titration was not allowed.[3] Additionally, one clinical expert who was consulted recommended the inclusion of a stopping rule at Week 28 in a scenario where up-titration was possible (Q4W non-responders at Week 16 are up-titrated to Q2W for an additional 12 weeks, at which point, response is assessed, and a decision is made to continue treatment).[3] Following Week 16/28 (depending on up-titration), clinical experts considered that it was reasonable to

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assume that patients who lose response during the Maintenance phase and maintain sustained non-response would stop treatment and move to BSC.[3] This approach aligns with that used in TA392 (in which patients who have been unresponsive for 12 consecutive weeks discontinue adalimumab treatment), NHS clinical practice and the clinical expert statement at the ACM, specifically: "*If the person's HS continued to not respond to secukinumab, then they would stop treatment*" (Section 3.11, DGD). It should be noted that the Induction phase in the model was for a duration of 16 weeks in line with the time point of the primary endpoint in the SUNNY trials.

To adequately capture this stopping rule, Novartis has introduced memory into the model by incorporating tunnel states. These additional health states track secukinumab patients with sustained non-response for an additional 12 weeks of treatment. The introduction of tunnel states allows for estimating the probability that patients remain non-responsive before discontinuing treatment. It also accounts for the possibility of patients with an initial non-response regaining response and transitioning out of these tunnel states into the responder health states (See Comment Response 4 and Table 3).

For transparency, Table 4 and Table 5 display the impact on the ICERs, excluding the stopping rule when up-titration is included or excluded, respectively.

Table 4: ICERs for the Company's revised base-case following DGD and removal of the stopping rule (probabilistic) – inclusion of up-titration (Company-preferred approach)

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Revised base-case following DGD							
BSC	[redacted]	22.699	[redacted]	-	-	-	-
SEC	[redacted]	22.699	[redacted]	[redacted]	0.000	[redacted]	£54,070
Scenario excluding the stopping rule							
BSC	[redacted]	22.758	[redacted]	-	-	-	-
SEC	[redacted]	22.758	[redacted]	[redacted]	0.000	[redacted]	£45,078

Abbreviations: BSC: best supportive care; DGD: Draft Guidance Document; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab.

Table 5: ICERs for the Company's revised base-case following DGD and removal of the stopping rule (probabilistic) – exclusion of up-titration.

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Revised base-case following DGD							
BSC	[redacted]	22.752	[redacted]	-	-	-	-
SEC	[redacted]	22.752	[redacted]	[redacted]	0.000	[redacted]	£60,898
Scenario excluding the stopping rule							
BSC	[redacted]	22.777	[redacted]	-	-	-	-

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	SEC	[redacted]	22.777	[redacted]	[redacted]	0.000	[redacted]	£46,772

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab.

7

Transition probabilities for the secukinumab arm (mismatch between the predicted and observed response rates at Week 16 (DGD Section 3.13)

Novartis acknowledges the Committee's concerns about an initial mismatch between the observed Week 16 HiSCR50 rates in the SUNNY trials and the predicted response rates of the Company's model. We have investigated this further and can confirm that this initial mismatch is a result of the initial skewed distribution of patients across the HiSCR states in the model, with all patients starting in the HiSCR<25 health state, interacting with the averaged transition probabilities during the Induction phase.

The approach of generating average transition probabilities was used because the multinomial model allows for a more robust estimation of transition probabilities by considering the observed transition counts across multiple 4-week cycles of the trial. Therefore, by analysing the data collectively, the overall trend of transitions in the trial may be captured rather than fluctuations in any 4-week period. This smoothing effect reduces the impact of random fluctuations in transition counts within specific cycles and provides a more reliable estimate of the average transition probabilities over a longer period.

In light of these considerations and in order to address the Committee's concerns, Novartis has revised its base-case to include per 4-week cycle transition probabilities for the Induction phase of the model (for both BSC and secukinumab) while maintaining average 4-weekly transition probabilities for longer-term transitions beyond Week 16. Beyond Week 16, it is noted that the overall number of transitions used to generate the transition probabilities decreased over the course of the SUNNY trials; between Week 12 and Week 16, 323 transitions were recorded compared with 131 between Week 48 and Week 52. As such, there is more value in maintaining average 4-weekly transition probabilities beyond Week 16 as the per-cycle transition probabilities become increasingly uncertain over this time frame due to the decreasing patient numbers.

Model-predicted response rates for the secukinumab Q4W arm of the model as compared with the observed response rates from the SUNNY trials at Week 16 are presented in Table 6. It is worth noting that, given the current model structure deviates from the SUNNY trials beyond Week 16 (Induction phase), in that non-responders to secukinumab Q4W at Week 16 are either up-titrated to the Q2W dosing regimen or discontinue to BSC (depending on the model setting chosen), it was not possible to validate response rates for the secukinumab arm up to Week 52 using response rates from the SUNNY trials, because in the SUNNY trials patients did not discontinue secukinumab at Week 16, irrespective of response or non-response, but were maintained on their blinded, randomised dose until Week 52.

Table 6: Validation of model-predicted response rates for secukinumab Q4W (per 4-week cycle transition probabilities) against the observed SUNNY data at Week 16,

Source	HiSCR≥75	HiSCR50–74	HiSCR25–49	HiSCR<25
Novartis' model	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	
SUNNY trials (observed data)	47.0%		53.0%	

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Abbreviations: HiSCR: hidradenitis suppurativa clinical response; Q4W: every 4 weeks.

Table 7: Validation of model-predicted response rates for BSC (per 4-week cycle transition probabilities) against the observed SUNNY data at Week 16

Source	HiSCR≥75	HiSCR50–74	HiSCR25–49	HiSCR<25
Novartis' model	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	
SUNNY trials (observed data)	32.9%		67.1%	

Abbreviations: BSC: best supportive care; HiSCR: hidradenitis suppurativa clinical response.

The impact on the ICER of using per-cycle transition probabilities for the Induction phase (included in the revised base-case) of the model (for both BSC and secukinumab) are shown in Table 8 (including up-titration – company-preferred approach) and Table 9 (excluding up-titration) for transparency.

Table 8: ICERs for the Company's revised base-case following DGD and a scenario using per-cycle transition probabilities during the Induction phase (probabilistic) – inclusion of up-titration (Company-preferred approach)

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Revised base-case following DGD							
BSC	[redacted]	22.699	[redacted]	-	-	-	-
SEC	[redacted]	22.699	[redacted]	[redacted]	0.000	[redacted]	£54,070
Scenario using average (four-weekly) transition probabilities up to Week 16							
BSC	[redacted]	22.765	[redacted]	-	-	-	-
SEC	[redacted]	22.765	[redacted]	[redacted]	0.000	[redacted]	£54,357

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab.

Table 9: ICERs for the Company's revised base-case following DGD and a scenario using the per 4-week transition probabilities during induction (probabilistic) – exclusion of up-titration

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Revised base-case following DGD							
BSC	[redacted]	22.752	[redacted]	-	-	-	-
SEC	[redacted]	22.752	[redacted]	[redacted]	0.000	[redacted]	£60,898
Scenario using average (four-weekly) transition probabilities up to Week 16							
BSC	[redacted]	22.812	[redacted]	-	-	-	-

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	SEC	[redacted]	22.812	[redacted]	[redacted]	0.000	[redacted]	£58,546

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab.

8

Transition probabilities for BSC arm (DGD Section 3.12)

Two of the key concerns raised by the Committee in the DGD were:

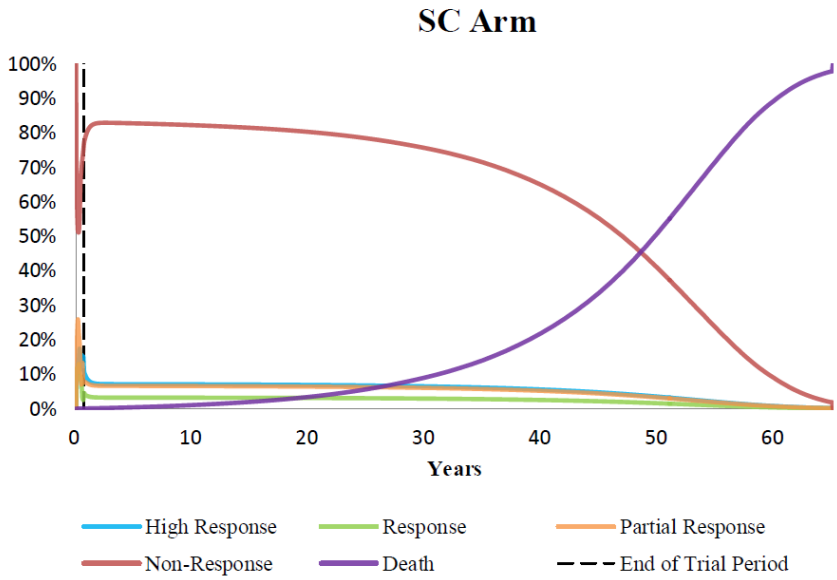
1. Plateauing of the BSC response curve; due to this, the Committee would like to see a scenario where a declining proportion of people in the response state of the BSC arm is modelled over time
2. Further validation of the model output with clinical expert input to support the choice of best source of data to be used

These are discussed in turn below.

Plateauing of the BSC response curve

Novartis acknowledges the Committee's concerns regarding the plateauing of the BSC response curves in the Company and EAG base-case. We would like to clarify that the plateau is a result of extrapolating a single matrix of transition probabilities over the remaining model time horizon, leading to an effective steady state of the BSC response curve until general population mortality increases in older age. It should be noted that the same trend was observed in the Company submission of TA392, as shown in Figure 1. Further, the plateau does not mean that patients cannot regain or lose response over time, but rather that this is the average proportion of responders over time, with patients still able to transition between HiSCR health states over the time horizon.

Figure 1: Markov Trace for BSC in TA392 (reproduction of Figure 25 of the Company Submission in TA392)



BSC represents SC

Abbreviations: BSC: best supportive care; SC: standard of care.

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Scenario in which a declining proportion of people in the response state of the BSC arm is modelled over time

In response to the Committee's request for a scenario in which the proportion of people in the response and high response health states decreases over time in the BSC arm, Novartis considers the PIONEER II study most suitable to inform the requested scenario.[5] This approach was deemed appropriate based on the best available data from the literature, clinician input elicited following the DGD and additional data from the SUNNY trials.

Clinical experts consulted by Novartis following supply of the DGD were asked to comment on the generalisability between PIONEER II and the SUNNY trials.[3] While acknowledging the existence of some differences in baseline characteristics, particularly with respect to prior surgery and Hurley stage, clinical experts noted that these differences likely reflected changes in clinical practice over the intervening years between the time when the PIONEER II study was conducted and the time when the SUNNY trials were conducted, particularly in terms of an increased use of surgery in the management of HS. The clinical experts also highlighted that the differences in baseline disease severity as measured by Hurley stage may be due to the variance in prior surgery, with patients in the SUNNY trials having more moderate disease (Hurley stage II) than patients in PIONEER II possibly due to recent prior surgery and previous biologics.[3] Clinical experts further emphasised that Hurley stage is not typically used to measure inflammatory burden in HS and that a comparison using Hurley stage between trials is not considered robust.[3] It was also noted that the trial inclusion criteria for disease severity was based on inflammatory burden and not on Hurley stage.[3] Overall, clinical experts considered that it was reasonable to use data from PIONEER II as a proxy for the population in the SUNNY trials.[3]

To further support the clinical validation, response rates for the placebo arm of the SUNNY trials at Week 16, categorised by Hurley stage and prior surgery are presented in Table 10. The results indicate that the observed response rates were similar regardless of Hurley stage and prior surgery, providing further justification for the use of PIONEER II data.

Table 10: HiSCR50 response rates for placebo at Week 16 from the SUNNY trials by Hurley stage and prior surgery

	SUNNY trials (n=363)
Response according to Hurley stage	
Stage II	[redacted]
Stage III	[redacted]
Response according to prior surgery	
No prior surgery	[redacted]
Prior surgery	[redacted]

Abbreviations: HiSCR: hidradenitis suppurativa clinical response.

Therefore, to model a scenario in which a declining proportion of people in the response state of the BSC arm is modelled over time (i.e., transitions from response categories to the non-response health state), the risk of loss of response estimates from the PIONEER II study was used. Figure 2 shows that among the placebo group, 44 out of 151 patients (29.1%) were responders (HiSCR ≥50) at Week 12. However, by Week 36, only 24 out of 151 patients (15.9%) maintained their response. This indicates that within the 24-week period between Weeks 12 and 36, 20 out of the initial 44 responders (45.5%) on placebo lost their response. This 24-week probability of losing

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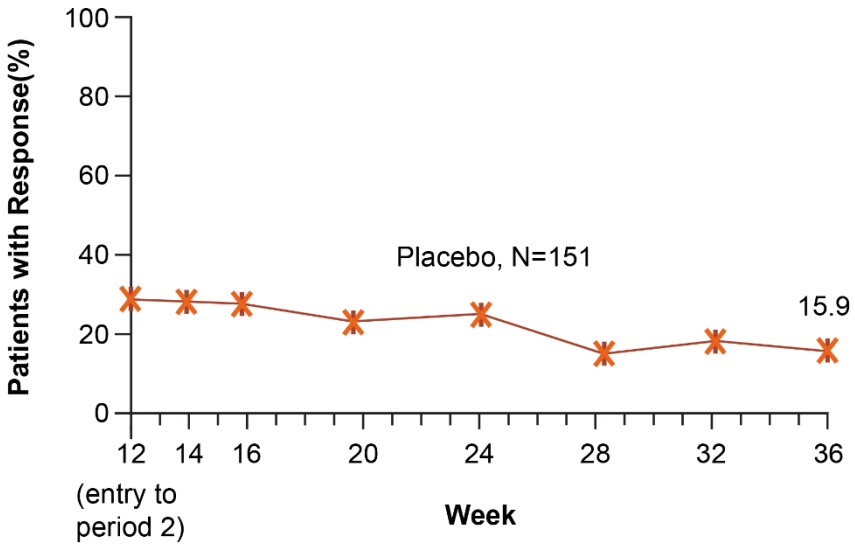
response was then converted into a 4-week probability, resulting in a value of 9.61%. This probability was used in the model to account for the likelihood of patients transitioning from various response categories to non-response. Novartis notes that this approach to modelling long-term transitions in the BSC arm of the model mirrors the approach taken in the original base-case prior to TE and further emphasises that this is the only feasible, evidence-based approach of modelling the requested scenario using available data from the literature. Therefore, any alternatives would rely heavily on arbitrary inputs or assumptions, lacking sufficient justification.

The impact of using the risk of loss of response estimates based on observed data from the PIONEER II study on the ICER is provided in Table 11 and Table 12. The results of these scenarios revert the model structure for the BSC arm to the structure prior to TE and then apply the constant loss of response data from PIONEER II. Additionally, the declining proportion of people in the response state of the BSC arm modelled over time is demonstrated in Figure 3 for transparency.

Figure 2: Patients assigned to placebo in Period 1 and reassigned to placebo in Period 2 in the PIONEER II trial



Source: Adapted from Jemec *et al*., (2019).[5]

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Figure 3: Health state occupancy over time for the BSC arm using the risk of loss of response estimates observed in PIONEER II to inform health state transitions during the Maintenance phase (Weeks 16–52, Week 52+)

Abbreviations: BSC: best supportive care; HiSCR: hidradenitis suppurativa clinical response.

Table 11: ICERs for the Company's revised base-case following DGD and a scenario using BSC transitions based on risk of loss of response estimates from PIONEER II (probabilistic) – inclusion of up-titration (Company-preferred approach)

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Revised base-case following DGD							
BSC	[redacted]	22.699	[redacted]	-	-	-	-
SEC	[redacted]	22.699	[redacted]	[redacted]	0.000	[redacted]	£54,070
Scenario using risk of loss of response estimates from PIONEER II							
BSC	[redacted]	22.770	[redacted]	-	-	-	-
SEC	[redacted]	22.770	[redacted]	[redacted]	0.000	[redacted]	£52,618

Abbreviations: BSC: best supportive care; DGD: draft guidance document; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab.

Table 12: ICERs for the Company's revised base-case following DGD and a scenario using BSC transitions based on risk of loss of response estimates from PIONEER II (probabilistic) – exclusion of up-titration

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Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Revised base-case following DGD							
BSC	[redacted]	22.752	[redacted]	-	-	-	-
SEC	[redacted]	22.752	[redacted]	[redacted]	0.000	[redacted]	£60,898
Scenario using risk of loss of response estimates from PIONEER II							
BSC	[redacted]	22.750	[redacted]	-	-	-	-
SEC	[redacted]	22.750	[redacted]	[redacted]	0.000	[redacted]	£64,351

Abbreviations: BSC: best supportive care; DGD: draft guidance document; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab.

Further validation of the model output with clinical expert input

As stated in our response to TE, Novartis sought clinical expert opinion to elicit feedback on the most plausible response curves for BSC expected over time in UK clinical practice, specifically in the population modelled in the decision problem.[6] Four clinical experts were consulted, and their input was sought to assess the face validity of the predictions from different approaches. Three out of the four clinicians consulted expected the proportion of non-responders to be more aligned with predictions using the Company's approach (i.e., using transition probabilities from TA392) compared with predictions using the EAG approach (i.e., using the Week 16 data from the SUNNY trials over the lifetime horizon).[6] One clinician found it difficult to comment.[6]

In response to the Committee's concerns in the DGD, Novartis sought further clinical expert opinion via a face-to-face Ad Board and individual consultations (see DGD Response Comment 2) to determine the most appropriate approach to model the BSC arm and to provide further validation of response curves.[3]

All seven clinical experts strongly agreed (at the face-to-face Ad Board or separately during individual consultations) that predictions using the EAG approach were unrealistic, lacked face validity, and did not reflect the unmet need for this population, given the conventional treatment landscape has been unchanged since TA392.[3] Clinical experts at the Ad Board and some individual clinical experts commented separately that the response curve using the EAG approach underestimated the unmet need for this population and further commented that if such response was observed in practice, there would be no need for therapies beyond conventional treatment.[3] Clinical experts felt that the prediction using the Company's approach (i.e., using data from PIONEER II as was used in TA392) were more plausible and reflected better the unmet need in this population, but highlighted the uncertainty.[3]

Comparison with observed data from PIONEER II (proportion of responders defined as HiSCR≥50).

As highlighted by the EAG, the placebo arms of the PIONEER II and SUNNY trials are broadly similar. Therefore, comparing model predictions to the placebo arm of PIONEER II up to Week 36 can be informative to determine which approach is the most appropriate.

It can be observed from Figure 4 that predictions using the Company's approach (i.e., using the SUNNY trials transitions up to Week 16, followed by transitions from TA392 between Week 16 and Week 36) result in similar proportions of responders at Week 16 (30.5%) and likewise at Week 36 (14.8%) when compared to PIONEER II (Week 16: 30.7%; Week 36: 15.9%). This stands in sharp

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contrast with the EAG's approach (i.e., using the SUNNY trials transitions up to Week 36), in which the proportion of responders predicted starkly deviates from both the Company's predictions and PIONEER II data after Week 16. Moreover, at Week 36, the proportion of responders is considerably higher (36.7%), approximately 2.5 times higher compared with the Company's approach.

Figure 4: Responder (HiSCR≥50) distribution across time horizon with the EAG's approach, in PIONEER II and in the Company's approach

Abbreviations: EAG: External Assessment Group; HiSCR: hidradenitis suppurativa clinical response.

Comparison with predictions in TA392 (proportion of responders according to HiSCR≥25).
In addition to the comparison provided above, model predictions reported in TA392 for the BSC arm were compared with the Company's approach and the EAG's approach (Figure 5). This comparison comes with an important caveat, however. The model predictions reported in TA392 were from the model prior to the first ACM, whereas the data from TA392 used in the secukinumab model were from revised data submitted in the response to the appraisal consultation document (ACD) and implemented in the final TA392 model. Nevertheless, the TA392 pre-ACD model was considered a useful framework for the validation of the two approaches, given that clinical experts consulted by Novartis following the DGD emphasised that the model predictions in TA392 were still valid and applicable because the conventional treatment landscape has remained unchanged since TA392 was published.[3]

The TA392 Pre-ACD reported the proportion of responders (HiSCR≥25) at Week 36, Year 5 and Year 10. It can be clearly seen in Figure 5, that the predictions made using the EAG approach considerably differed from those in TA392 pre-ACD, whereas the predictions using the Company's approach were more aligned with TA392. However, as noted, the Company's approach uses data included only in the post-ACD TA392 model for which the proportion of responders were not further reported.

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Figure 5: Responder (HiSCR≥25) distribution across time horizon with the EAG's approach, in TA392 and in the Company's approach

Abbreviations: EAG: External Assessment Group; HiSCR: hidradenitis suppurativa clinical response.

Comparison with predictions in TA392 (proportion of non-responders according to HiSCR<25) over a lifetime horizon

Using the health state occupancy reported in TA392 as a useful reference point, another way to visualise differences between the Company's approach and the EAG's approach over a longer time horizon is to compare the proportion of non-responders (Figure 6). Again, the same caveat regarding difference between the pre- and post-ACD TA392 models applies.

The proportion of non-responders in TA392 over the lifetime was digitised using DigitizIt (as values are not directly provided; blue line) and compared with predictions using the EAG's approach (orange line) and the Company's approach (red line). Again, the Markov traces clearly highlight the mismatch between the EAG's approach and predictions in TA392 for BSC over the lifetime horizon of the model.

Figure 6: Non-responder (HiSCR<25) distribution across time horizon with the EAG's approach, in TA392 and in the Company's approach

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	 **Abbreviations:** EAG: External Assessment Group; HiSCR: hidradenitis suppurativa clinical response. **Comparison of QALYs generated for the placebo arm in TA392 and using the company's and EAG approach** Comparing the total of number of QALYs generated for the placebo arm in TA392 to those predicted in this appraisal for placebo using the company's and EAG approach may also provide a useful reference point. In TA392, a total number of 11.63 discounted QALYs were reported for patients on placebo/BSC. We therefore compared the total number of discounted QALYs predicted in the model using the same assumptions as in TA392; this includes the following changes (1) setting the age-utility adjustment to 1 (to align with approach in TA392), (2) using TA392 utility data (to align with utility values used in TA392) and (3) remove disutility due to AEs (not included in TA392). In summary, when aligning with inputs/assumptions from TA392, the model predicts a total of 11.51 discounted QALYs using the company's approach (e.g using transition probabilities derived from PIONEER-2) compared with 13.50 discounted using the EAG approach (extrapolating transition probabilities from the SUNNY trial over lifetime). Therefore, the EAG approach generate almost 2 discounted QALYs more than what was used in decision-making in TA392 for the placebo/BSC arm. In contrast, the estimate of total discounted QALYs using the company's approach is more aligned with those reported in TA392. We therefore believe that this comparison of total number of QALYs provides further arguments in favour of our approach. **Summary** In summary, while Novartis recognises the uncertainty, the validation process involving clinical expert input consistently supported the use of the Company's approach to use transition probabilities from TA392, as it demonstrated greater face validity and was better aligned with the observed data from PIONEER II and predictions accepted in TA392. These findings reinforce the reliability of the approach taken by Novartis and substantiate the chosen modelling scenario for the

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BSC arm in the decision problem. Nonetheless, a scenario using an arbitrary 10% increase in BSC loss of response probability after Week 52 is presented in Table 13 (including up-titration) and Table 14 (excluding up-titration) to inform the Committee's decision making.

Table 13: ICERs for the Company's revised base-case following DGD and a scenario using an arbitrary 10% increase in BSC loss of response probability after Week 52 (probabilistic) – inclusion of up-titration (Company-preferred approach)

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Revised base-case following DGD							
BSC	[redacted]	22.699	[redacted]	-	-	-	-
SEC	[redacted]	22.699	[redacted]	[redacted]	0.000	[redacted]	£54,070
Scenario using an arbitrary 10% increase in BSC loss of response probability after Week 52							
BSC	[redacted]	22.786	[redacted]	-	-	-	-
SEC	[redacted]	22.786	[redacted]	[redacted]	0.000	[redacted]	£53,512

Abbreviations: BSC: best supportive care; DGD: draft guidance document; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab.

Table 14: ICERs for the Company's revised base-case following DGD and a scenario using an arbitrary 10% increase in BSC loss of response probability after Week 52 (probabilistic) – exclusion of up-titration

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Revised base-case following DGD							
BSC	[redacted]	22.752	[redacted]	-	-	-	-
SEC	[redacted]	22.752	[redacted]	[redacted]	0.000	[redacted]	£60,898
Scenario using an arbitrary 10% increase in BSC loss of response probability after Week 52							
BSC	[redacted]	22.758	[redacted]	-	-	-	-
SEC	[redacted]	22.758	[redacted]	[redacted]	0.000	[redacted]	£60,214

Abbreviations: BSC: best supportive care; DGD: draft guidance document; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab.

9

Treatment-specific health-state utilities (DGD Section 3.14)

Novartis acknowledges the Committee's consideration of treatment-specific utility values in the non-response health state for secukinumab and BSC arms.

During TE, Novartis provided clinical evidence on the individual components which together comprise the HiSCR endpoint, by treatment, to support treatment differences within health states. Results from a repeated measures regression model of utilities (EuroQoL-5 dimensions [EQ-5D]),

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with interaction terms between treatment and health state up to Week 16, were also provided. Both showed strong and conclusive evidence in support of the use treatment-specific utilities for some health states, if not all: in particular, the non-response health state.

Results demonstrated that patients in the non-response health state treated with secukinumab have higher quality of life compared with patients with no response on placebo using data up to Week 16. The Committee therefore considered that treatment-specific utility values should only be used up to Week 16 in the model as long-term placebo data do not exist (due to the trial design of the SUNNY trials, specifically the ethical implications of keeping patients on placebo for >16 weeks) which would directly support treatment-specific utility values after Week 16.

Novartis notes that the utility values for placebo in the PIONEER II trial were 0.557 at Week 12 and 0.520 at Week 36, suggesting that quality of life on placebo deteriorates with time. While specific data beyond Week 16 for BSC may be lacking, due to the ethical requirement to minimise time on placebo in the trial design, longer-term data are available for secukinumab up to Week 52 in the SUNNY trials. The data (see below) show that the clinical benefit and utility values reported up to Week 16 are maintained in the long-term.

In response to the DGD and to support the use of treatment-specific utility beyond Week 16, additional data are provided on (1) the mean percentage change in AN count from baseline to Week 28 and Week 52 and (2) the mean EQ-5D score in each HiSCR health state at Weeks 16 and Week 52.

Clinical data

Table 15 presents the mean percentage change in AN count from baseline in each HiSCR health state at Week 16. Similar to the data presented in Table 5 of the Company's response to TE (where n numbers report the total number of evaluations of AN count), the results below showed that the reduction in the mean AN count from baseline for the secukinumab treatment arms for the non-response health state ([redacted]% versus [redacted]% for secukinumab Q2W and Q4W, respectively) compared with an increase for placebo ([redacted]%) is statistically significant. These results indicate that patients on secukinumab in the non-responder health state have better outcomes in terms of reduction in AN count than patients on placebo in the same health state.

Table 15: Mean percentage change from baseline in AN count at Week 16 in each HiSCR health state

Treatment	Mean (SD) percentage change in AN count			
	HiSCR<25	HiSCR25–49	HiSCR50–74	HiSCR≥75
SEC Q2W (n=361)	[redacted]	[redacted]	[redacted]	[redacted]
SEC Q4W (n=360)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=363)	[redacted]	[redacted]	[redacted]	[redacted]

* P-values <0.05 versus placebo. n indicates patient numbers in each treatment arm.
Abbreviations: AN: abscesses and inflammatory nodule; HiSCR: hidradenitis suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation; SEC: secukinumab.

Data at Week 28 (Table 16) and Week 52 (Table 17) show that the effect of secukinumab in the long term is consistently better than that observed at Week 16, supporting the contention that the

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benefit of secukinumab is maintained in the long-term, including in the non-response health state for which treatment-specific utilities are applied.

Table 16: Mean percentage change from baseline in AN count at Week 28 in each HiSCR health state

Treatment	Mean (SD) percentage change in AN count			
	HiSCR<25	HiSCR25–49	HiSCR50–74	HiSCR≥75
SEC Q2W (n=304)	[redacted]	[redacted]	[redacted]	[redacted]
SEC Q4W (n=306)	[redacted]	[redacted]	[redacted]	[redacted]
SEC Pooled (n=610)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AN: abscesses and inflammatory nodule; HiSCR: hidradenitis suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation; SEC: secukinumab.

Table 17: Mean percentage change from baseline in AN count at Week 52 in each HiSCR health state

Treatment	Mean (SD) percentage change in AN count			
	HiSCR<25	HiSCR25–49	HiSCR50–74	HiSCR≥75
SEC Q2W (n=254)	[redacted]	[redacted]	[redacted]	[redacted]
SEC Q4W (n=255)	[redacted]	[redacted]	[redacted]	[redacted]
SEC Pooled (n=509)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AN: abscesses and inflammatory nodule; HiSCR: hidradenitis suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation; SEC: secukinumab.

EQ-5D

Similarly, mean EQ-5D utility values up to Week 16 and Week 52 are provided in Table 18 and Table 19, respectively. The data show that the EQ-5D score in each HiSCR category are maintained in the long-term while patients are on secukinumab. Although data are not available for placebo in the SUNNY trials after Week 16, the utility values for placebo in the PIONEER II trial were 0.557 at Week 12 and 0.520 at Week 36, suggesting that quality of life on placebo deteriorates with time.

Table 18: Mean EQ-5D utility values from SUNNY trials Weeks 2–16 pooled, all patients

Treatment	Mean EQ-5D Utility (Number of Observations, Standard Error)			
	HiSCR<25	HiSCR25–49	HiSCR50–74	HiSCR≥75
SEC Q2W	[redacted]	[redacted]	[redacted]	[redacted]
SEC Q4W	[redacted]	[redacted]	[redacted]	[redacted]

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Placebo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D: EuroQoL-5 dimensions; HiSCR: hidradenitis suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks; SEC: secukinumab.

Table 19: Mean EQ-5D utility values from SUNNY trials Weeks 2–52 pooled, all patients

Treatment	Mean EQ-5D Utility (Number of Observations, Standard Error)			
	HiSCR<25	HiSCR25–49	HiSCR50–74	HiSCR≥75
SEC Q2W	[redacted]	[redacted]	[redacted]	[redacted]
SEC Q4W	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D: EuroQoL-5 dimensions; HiSCR, hidradenitis suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks; SEC: secukinumab.

Summary

In summary, we believe that the evidence presented as part of this response strongly supports the rationale for applying treatment-specific utility values during the Maintenance phase of the model, for the non-response health state in the model. By capturing the potential ongoing benefits of secukinumab treatment, the model better reflects the sustained clinical response and quality of life improvement observed in the trial and expected with secukinumab. Considering the additional data provided, we urge the Committee to reconsider their position. Given this, the Novartis revised base-case following DGD Response does not include any changes to the approach for utility values. However, to assess the impact on the ICER of using treatment-pooled utility values for all health states including the non-response health state during the Maintenance phase, scenarios are shown in Table 20 (including up-titration; the Company-preferred approach) and Table 21 (excluding up-titration) for transparency.

Additionally, while specific data beyond Week 16 for BSC may be lacking, due to the ethical requirement to minimise time on placebo in the trial design of the SUNNY trials, the assumption of maintaining utility values for BSC aligns with the nature of supportive care interventions, which are not expected to prove efficacious, especially when limited to the Committee's preference of trial-permitted therapies only, which has been incorporated in the revised base-case.

We would also like to highlight that the treatment-specific utility values applied in the non-response health state only provide a benefit to patients who are receiving secukinumab treatment in the given cycle and incurring the cost of treatment as a result. Patients who remain in the non-response health state for 12 weeks are discontinued from treatment in the revised base-case, and therefore move to BSC, where the treatment-specific utility for patients on secukinumab no longer applies.

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Table 20: ICERs for the Company's revised base-case following DGD and a scenario using treatment-pooled utility values for all health states including the non-response health state during the Maintenance phase (probabilistic) – inclusion of up-titration (Company-preferred approach)

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Revised base-case following DGD							
BSC	[redacted]	22.699	[redacted]	-	-	-	-
SEC	[redacted]	22.699	[redacted]	[redacted]	0.000	[redacted]	£54,070
Scenario using treatment-pooled utility values for all health states during the Maintenance phase							
BSC	[redacted]	22.723	[redacted]	-	-	-	-
SEC	[redacted]	22.723	[redacted]	[redacted]	0.000	[redacted]	£77,311

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab.

Table 21: ICERs for the Company's revised base-case following DGD and a scenario using treatment-pooled utility values for all health states including the non-response health state during the Maintenance phase (probabilistic) – exclusion of up-titration

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Revised base-case following DGD							
BSC	[redacted]	22.752	[redacted]	-	-	-	-
SEC	[redacted]	22.752	[redacted]	[redacted]	0.000	[redacted]	£60,898
Scenario using treatment-pooled utility values for all health states during the Maintenance phase							
BSC	[redacted]	22.730	[redacted]	-	-	-	-
SEC	[redacted]	22.730	[redacted]	[redacted]	0.000	[redacted]	£81,316

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab.

10

Surgery costs

Novartis acknowledges the Committee's concerns over the most appropriate surgery costs to include in the decision-making model, which mirrors the concerns of the EAG at TE.

To further validate which approach is the most appropriate to modelling surgery costs, Novartis consulted clinical experts following the DGD (See DGD Response Comment 2).[3] Experts were asked to comment on which of the two approaches (Company's approach [in line with that used in TA392, proposed by the Evidence Review Group and accepted by the Committee] and the approach used by the EAG in this appraisal [using distribution of surgeries/procedures from the

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NHS reference cost non-specific to HS]) most closely reflected the cost for the mix of surgeries/procedures for HS in NHS clinical practice for the population modelled in the decision problem.

A follow-up email was sent to all seven clinical experts (email provided in the reference pack for transparency). Clinical experts were asked to comment on which approach was the most appropriate and reflective of the cost of surgery/procedure in HS. To reduce bias, approaches were referred to as Approach 1 and 2 (rather than the Company's approach and EAG's approach, respectively). Responses were received from 3 out of the 7 clinical experts due to the holiday period, and deadline to respond to the DGD.

In summary, all three clinical experts agreed that while neither approach is perfect, Approach 1 was considered the most reflective of the costs for the mix of surgeries/procedures for HS in NHS clinical practice.[3] One clinical expert further pointed out that the surgery costs may be underestimated if patients with moderate to severe HS could not have adalimumab (as there are no other biologics recommended by NICE for this indication).[3] Consistent with the feedback received at TE, there was an indication that most HS surgeries would fall under the day case intermediate category (wide excision of 1 skin region), day case minor category (incision and drainage, and narrow wide excision) and non-elective short stay procedures.[3] Another clinical expert noted that while Approach 1 (the Company's approach based on TA392) was favoured over Approach 2 (the EAG's approach), the day case intermediate and minor procedures could be evenly split, incorporating both Approach 1 and 2.[3]

Additionally, if we compare the current EAG's estimate (£1,217) for this appraisal (based on the NHS reference costs from 2020–2021) with the ERG's estimate of surgery costs (£1,525.74) in TA392, which is based on NHS reference costs from 2013–2014, the EAG's approach would suggest that surgery costs have decreased by 20% compared with that which was accepted by the Committee in TA392. However, considering inflation since TA392 (2016), it is highly unlikely that costs would have decreased between the time of TA392 and the secukinumab appraisal, suggesting that the EAG's estimate lacks face validity and underestimates surgery costs.

For all the reasons stated above, the Novartis revised base case following the DGD maintains the approach to surgery costs adopted following TE, based on the cost of surgery proposed by the ERG and accepted by the Committee in TA392. For transparency, however, an additional scenario analysis has been conducted and provided in Table 22 and Table 23 assuming an equal split between day case minor and intermediate procedures as per clinical expert advice provided above.

Table 22: ICERs for the Company's revised base-case following DGD and scenario excluding surgery costs (probabilistic) – inclusion of up-titration (Company-preferred approach)

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. Lys	Inc. QALYs	ICER
Revised base-case following DGD							

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	BSC	[redacted]	22.699	[redacted]	-	-	-	-
	SEC	[redacted]	22.699	[redacted]	[redacted]	0.000	[redacted]	£54,070
	Scenario assuming equal split between day case minor and intermediate procedures							
	BSC	[redacted]	22.767	[redacted]	-	-	-	-
	SEC	[redacted]	22.767	[redacted]	[redacted]	0.000	[redacted]	£54,962

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab.

Table 23: ICERs for the Company's revised base-case following DGD and scenario excluding surgery costs (probabilistic) – exclusion of up-titration

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. Lys	Inc. QALYs	ICER
Revised base-case following DGD							
BSC	[redacted]	22.752	[redacted]	-	-	-	-
SEC	[redacted]	22.752	[redacted]	[redacted]	0.000	[redacted]	£60,898
Scenario assuming equal split between day case minor and intermediate procedures							
BSC	[redacted]	22.746	[redacted]	-	-	-	-
SEC	[redacted]	22.746	[redacted]	[redacted]	0.000	[redacted]	£61,744

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; QALYs: quality-adjusted life years; SEC: secukinumab.

11

Outpatient resource use rates (DGD Section 3.18)

With respect to the Committee's choice expressed in the DGD "*the Committee conservatively preferred the use of outpatient visit costs from the EAG base case, which aimed to reduce the possibility of double counting*" (Section 3.18), Novartis would wish to remind the Committee that the initial suggestion of double counting raised in the EAR stemmed from an inadvertent rewording of the description of one resource use category in the Company Submission during drafting. The original source numbers from TA392 were unambiguous in their description and therefore clear that there was no double counting. Given this situation has only arisen due to a drafting error rather than due to any underlying problem with the source data, Novartis would invite the Committee to reconsider their conclusion on this point.

Novartis further notes that the questionnaire and the explanation of the calculation of the model inputs from the raw results are available in Committee papers 2 for TA392, (Appendix C, PDF page 53 of https://www.nice.org.uk/guidance/ta392/documents/Committee-papers-2). Of note, examination of the results for each relevant physician survey question further reaffirms that there is no double counting possible as the questions are clearly worded to avoid this. Specifically:

- *Average number of hospitalisations for those that underwent at least one in-patient HS surgical procedure (Q13b) (B)*
- *Average out-patient visits involving HS surgical procedure for those that had at least one out-patient HS surgical procedure (Q13c)*

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	• *Average number of hospitalisations for those that had at least one hospitalisation not involving HS surgical procedure (Q13d)* • *Average number of A&E visits for those that had at least one non-surgical A&E visit (Q13e)* • *Average number of wound care visits following surgery for those that had at least one visit to wound care (Q13f)* • *Average number of wound care visits non-surgery related for those that had at least one non-surgery related wound care visit (Q13g)* • *Average number of routine outpatient visits (Q13h)* Clinical experts consulted during the face-to-face Ad Board (topic not covered during the individual consultations due to time constraints further indicated that the difference in the number of outpatient visits between non-responders and high responders using the EAG proposed approach was lower than would be expected (3.1 for high-responders versus 4.68 for non-responders [e.g., difference of 1.58 visits]) and considered the difference in outpatient visits as reported in the survey (4.11 versus 6.92 [e.g., difference of 2.81 visits]) to be more appropriate.[3] Considering the additional clarification provided, we urge the EAG/Committee to reconsider their position. Given this, the Novartis revised base-case following DGD Response does not include any changes to outpatient resource use rates.

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 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) 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 draft guidance document, please submit these separately.

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Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory Committees.

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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):	[redacted] (clinical expert on NICE panel)

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	1. Small grant to make a patient information film on the use of surgery in Hidradenitis supurativa- NOVARTIS- this is complete and the output (the film) not linked or inputted to by NOVARTIS 2. Honoraria for taking part in advisory panels: Sept 22-March 23 NOVARTIS- this was not directly related to the product being assessed and was a Europe wide collaboration to set up an HS website to help inform other health care professionals about HS- this is completed.
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. 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	I am concerned that this recommendation leaves a group of patients with moderate to severe disease in a medical landscape with very limited prospect for improvement. I am concerned that

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	the lack of patient representative on the panel may have meant that the impact of this disease has not been fully explored by members of the committee.
2	The issues discussed around BSC during the meeting remain problematic. However it is very unlikely that there will be better evidence to gain better insight into this heterogeneous group of treatments in such a way that would allow a comparison owing to issues with objective scoring in HS and different clinical phenotypes.
3	As a clinician I feel that not having the option to judiciously increase the dose of secukinumab would be suboptimal but would like to flag that I feel exploration of this topic by NICE is important. In psoriasis, for example, access to Secukinumab at a higher dose for heavy patients was offered after NICE approval by Novartis and despite the fact that this is offered cost neutral, my trust will not allow me to access the higher dose as it is not NICE approved. Therefore discussion of this by the NICE committee is important. I remain keen to have this as an option available to me ideally in clinical practice as many of the patients with HS are heavy with BMIs >35 meaning that higher doses may be required to have an effect on the inflammatory aspect of the disease.
4	Surgical costs: whilst I feel that estimating the surgical costs in patients who cannot be treated with Adalimumab or who have failed Adalimumab is difficult, and perhaps neither of the approaches presented are ideal as both are likely grossly underestimating the amount of surgery such a patient would need, I feel that approach 1 is probably closest to what such a patient might experience. However the amount of surgery the patient would need would be higher (as most of the procedures would not alter the clinical progression of the disease). Where patients might be able to have disease altering surgery (elective major, elective intermediate and day case major and intermediate) this assumes that they are a suitable candidate for surgery (BMI of >35 and smoking may preclude this) and may offer some reduction in disease burden but the procedures are not only costly there is also an additional burden with associated dressings in the post op period.
5	I think the documented high placebo response in HS trials is of interest but likely to have an ongoing effect on trials in this condition
6	I strongly support the comment that switching patients from placebo arms to treatment arm is reasonable as it would be unethical to leave patients untreated with a mostly progressive disease.
7	

Insert extra rows as needed

Checklist for submitting comments

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- 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 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) 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.

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- 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.
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Single Technology Appraisal

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	N/A
Conflict	No
Comments on the DG:	

As a Consultant Dermatologist in the NHS for over 23 years I have seen the devastating effect of Hidradenitis in patients.
I was the lead in HS in [redacted] in the NHS England assigned unit and I have had first hand experience with patients severely affected by the horrible condition.
My current Trust was invoked in the clinical trials using Secukinumab in HS. We desperately need an alternative to Adalimumab. Only half the patients will respond and at best they will get half better.
There are those that cannot have anti TNF and they are the ones with significant comorbidities. Secukinumab provides a suitable effective and safe alternative. We are all used to it in psoriasis including its paediatric usage. Their Q2W dosing in above 90kg is already well established.
As many of my patients with HS have commented ' any improvement will be greatly appreciated ' for an awful disease.
However, I am not usually involved in commercial decisions but I do think the costs are rather high. I suppose that is something the manufacturer can work on.
In my humble opinion HS should be intervened early to prevent progression.

Name	[redacted]
Organisation	N/A
Conflict	No
Comments on the DG:	

Question: Has all of the relevant evidence been taken into account?
I have concerns that the published evidence, particularly on BSC in HS is very limited. In my view the Committee has underestimated the morbidity and costs of BSC in HS. Clinically, patients with Hurley stage 2-3 HS are often referred for, often quite radical, surgery. This is likely to be sequential surgery as plastic/general surgeons are not able to complete all the necessary surgery on one occasion. Also the costs of monitoring and supervision of patients with HS on BSC are very considerable. I am concerned that the Committee has underestimated the psycho-social and

clinical consequences of BSC for patients who have mod-severe HS. I am also concerned that the Committee has underestimated the financial costs of BSC in patients with severe HS, as the evidence is so poor, and clinical experience would indicate that these costs are greater than the evidence cited in these recommendations.

Question: Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
I am unclear why the Committee has concluded (section 3.4) that the 'clinical data was not aligned with the intended positioning'. I was involved as a PI in the SUNNY trials. As I understand it, in the SUNNY trials a proportion of patients (approximately 23%) had prior biologics exposure. This would reflect clinical practice in that most patients would be trialled on adalimumab initially, and then if failing adalimumab would then be offered either BSC or an alternative biologic (eg secukinumab). In addition, by definition, those patients who are trialled on adalimumab are biologics naive.

I don't understand why the Committee report (section 3.7) that 'This may favour secukinumab.' As a PI in the SUNNY trials, patients who needed concomitant medication were given that medication. If they continued to respond to secukinumab and con-meds, then the patients continued in the trial. If they did not respond, the patients would leave the trial. So the conclusion that 'people having the BSC treatments permitted in the SUNNY trials will have worse efficacy outcomes than people having BSC in clinical practice (section 3.7)', is incorrect (or at least highly speculative).

Question: Are the recommendations sound and a suitable basis for guidance to the NHS?
I am concerned that the Committee has not fully appreciated the physical / psychosexual and psycho-social consequences of living with severe HS whilst being treated with BSC. Patients with severe HS who have tried and failed adalimumab are very severely affected by their disease, and BSC is poorly defined and of highly variable efficacy in these patients. I have been involved as a PI in the open label extension SUNNY studies and for my patients (all of whom have been adalimumab failures), secukinumab was successful (and has remained successful) in managing their disease effectively.

Question: 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?
No.

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Secukinumab for treating moderate to severe hidradenitis suppurativa.

[ID4039]

EAG critique of the company's response to the Appraisal Consultation Document (ACD)

Produced by Aberdeen HTA Group

Authors Mekazin Tsehaye[1]
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Email: d.boyers@abdn.ac.uk

Date completed: **27 July 2023**

Contains: [redacted]

Version: **V1.0**

Overview of main issues post ACD

This report provides the EAG's brief commentary and critique of the company's (Novartis) submitted response to the appraisal consultation document (ACD) and in advance of the second appraisal committee (AC) meeting for this topic. The commentary focuses on issues of uncertainty and committee preferences raised following the first AC meeting and follows the order of issues discussed in the ACD. The main issues are summarised in Table 1, with remaining issues of disagreement elaborated on in the sections that follow.

Table 1: Summary of main issues for consideration at the 2nd AC meeting

Issue no.	ACD section	Issue	NICE ACD preferred assumption	Company preferred approach post ACD	EAG preferred approach post ACD
1	3.10	Up-titration of secukinumab dosing for non-responders to Q4W dose at week 16.	Up-titration should not be included in the base case model assumptions as it was not assessed in the SUNNY trials.	Company prefers to include up-titration in line with marketing authorisation but provide scenario analyses removing up-titration.	EAG prefers to remove up-titration because the true effectiveness of Q2W dose in an up-titrated subgroup is unknown.
2	3.11	Secukinumab stopping rules.	Patients with a sustained non-response to secukinumab would stop treatment. A stopping rule similar to that applied for adalimumab in TA392 would be reasonable (initial assessment at 12 weeks + reassessment every 3-6 months).	Two stopping rules are applied (no up-titration): 1) Non-responders (HiSCR<25) at the end of the induction phase of the model (week 16). 2) Sustained non-responders, defined as 3 consecutive cycles (tunnels) in the HiSCR<25 state.	The proposed stopping rules are implemented in the economic model as described.
3	3.12	Long-term BSC transition probabilities	Committee felt that plateauing of the BSC response curves in the	The company retains their preference to use BSC data from the PIONEER II study to	The EAG retains the preference to use 16-week data from the placebo arms of the SUNNY trials because of:

Issue no.	ACD section	Issue	NICE ACD preferred assumption	Company preferred approach post ACD	EAG preferred approach post ACD
			company and EAG base cases lacked face validity and wanted to see scenarios where BSC response reduces over time. Committee accepted EAG concerns that BSC effectiveness derived from both the SUNNY and PIONEER II trials may under-estimate the BSC effectiveness in UK clinical practice.	inform BSC long-term transitions. The approach was validated with the company's clinical experts. Scenario analyses reported for an arbitrary 10% loss in BSC response over 52 weeks.	1) Imbalances between the placebo arms of the PIONEER II and SUNNY studies that increase uncertainty. 2) Implied risk ratios of response at several time points from the EAG preferred approach are more aligned with the SUNNY trial outcomes. 3) The effectiveness of BSC may be underestimated because it ignores the effect of surgery or more active BSC treatments on HiSCR.
4	3.13	Transition probabilities for the secukinumab arm	EAG and company base case analyses over-estimated 16- and 52-week response probability (HiSCR 50-74 and ≥75) compared to data from the SUNNY trials.	Company applied per cycle transitions for secukinumab and BSC up to week 16 (induction phase) and average cycle transitions thereafter.	The company's revised approach accurately aligns health state occupancy with response data from the SUNNY trials up to week 16. Several modelling assumptions, including stopping rules prevent a direct comparison at week 52.

Issue no.	ACD section	Issue	NICE ACD preferred assumption	Company preferred approach post ACD	EAG preferred approach post ACD
5	3.14	Treatment specific utility values in the non-response state	Treatment specific HSUVs preferred in the non-response state only up until week 16, with treatment pooled HSUVs in all states thereafter.	The company retain their original preference to apply treatment specific HSUVs in the non-response state for the full model time horizon.	The EAG agree with the company that the use of treatment specific HSUVs in the non-response state is justified and supported by the available clinical data, including additional supporting evidence provided in response to the ACD.
6	3.15 & 3.16	BSC costs	Drug acquisition costs for BSC should be aligned with the placebo arm of the SUNNY trials and surgery costs should be included.	As per NICE ACD preference	Issue resolved.
7	3.16	Surgery costs	Given uncertainty surrounding HS surgery costs, the committee preferred the EAG's more conservative weighed average surgery cost (£1,217).	The company retain their preference to align costs with those included in TA392 (£2,402). The company provided an additional scenario analysis assuming an equal split between day case minor and intermediate procedures.	The EAG maintains its preference to apply weighed average surgery costs of £1,217, accounting for a mix of minor, moderate and major procedures (see details in EAG critique of company response to technical engagement).

Issue no.	ACD section	Issue	NICE ACD preferred assumption	Company preferred approach post ACD	EAG preferred approach post ACD
8	3.17	Hospital resource use rates	Committee preferred to keep the company hospital resource rates	No change	EAG aligned with company base case. Issue resolved.
9	3.18	Outpatient resource use rates	Committee preferred the EAG proposed outpatient resource use rates to avoid the risk of double counting	The company provide further re-assurance that outpatient resource use was not double counted.	On reflection, the EAG accept the company's position and are now satisfied that the risk of double counting is minimal.

Abbreviations: ACD: appraisal consultation document; BSC: best supportive care; Co. BC: company base case analysis; EAG: external assessment group; HiSCR: Hidradenitis Suppurativa Clinical Response; HSUV: health state utility values; ICER: incremental cost-effectiveness ratio; NICE: National institute for health and care excellence; Q2W: 2-weekly dose; Q4W: 4-weekly dose; QALY: quality adjusted life year

Issue 1: Up-titration of secukinumab Q4W dose to Q2W dose amongst patients who do not respond to Q4W dose

The company maintains its preference to include up-titration in line with the marketing authorisation for secukinumab and to provide patients and clinicians with another option to treat HS, particularly given the positioning post adalimumab. The company provide all analyses including and excluding up-titration for information.

The EAG acknowledges that there is an unmet need amongst patients failing to respond to the Q4W dose who have either failed or are unsuitable for adalimumab, and that patients and clinicians may welcome the opportunity to up-titrate dose to achieve a response. However, the company has not provided any evidence to support the effectiveness of the Q2W dose amongst those who are harder to treat, having already failed to achieve a response on the Q4W dose. The EAG therefore agrees with the committee conclusion that base case estimates of cost-effectiveness should be assessed without up-titration because the effectiveness of up-titration was not assessed in the SUNNY trials and is therefore unknown. However, the impact of up-titration on the ICER is likely to be small to moderate [redacted] *For example, the EAG note that removing up-titration leads to a modest increase in the ICER, ranging from approximately £1000 to £6000 depending on the scenario presented (see company response document to ACD).*

Issue 2: Secukinumab stopping rules.

Following the committee preferences outlined in the ACD, the company provided an updated economic model to implement stopping rules for secukinumab treatment due to non-response. The stopping rules were mostly aligned with those preferred by the committee for the assessment of adalimumab (TA392). Two stopping rules were implemented:

1) The proportion of the cohort in the non-response health state (HiSCR <25) at the end of cycle 4 (week 16) were discontinued from treatment and moved to BSC.
2) The proportion of the cohort at any point in the maintenance phase of the model who had a sustained non-response were also discontinued from treatment and moved to BSC. Sustained non-response was defined as spending three consecutive cycles (i.e., 12 weeks) in the non-response state. Memory was built into the model using tunnel

states to track the proportion of the cohort in the non-response state for three consecutive cycles.

The EAG is satisfied that the proposed stopping rules are implemented in the economic model as described. The initial decision to assess non-response at week 16 (as opposed to week 12 for adalimumab in TA392) is appropriate to align with the SUNNY trial induction phase. Defining a consistent non-response of three consecutive cycles without a response seems reasonable and is consistent with the approach taken in TA392. The EAG considered whether the resource use included in the model was sufficient to pragmatically implement the proposed stopping rules in UK clinical practice. Resource use associated with frequent outpatient visits and a total of between 4.5 to 8.7 consultations with healthcare professionals are included per year across different health states. The EAG is broadly satisfied that the current modelled resource use is mostly sufficient to pragmatically assess non-response in clinical practice.

Issue 3: BSC transition probabilities

The committee was concerned that plateauing of the BSC response curves in the company and EAG base cases lacked face validity. The committee noted EAG concerns that BSC extrapolations based on the placebo arm of the POINEER II study may under-estimate the effectiveness of BSC but wanted to see analyses where the BSC response reduced over time. The company retains their preference to use BSC data from the PIONEER II study to inform BSC long-term transitions. The approach was validated with the company's clinical experts who felt that the differences between PIONEER II (surgery use and hurley stage) would not preclude the use of the PIONEER II data. The company also report the result of a scenario analysis where an arbitrary 10% loss in BSC response is applied over 52 weeks.

The EAG acknowledges that the long-term effectiveness of BSC has an important impact on both the response curves for the secukinumab and BSC arms of the model. Different assumptions lead to substantial differences in the ICER, with higher BSC response rates leading to higher ICERs. The EAG acknowledges the committee concerns and agrees that a plateauing of the BSC response curve would be unrealistic if patients received treatment as per BSC defined in the placebo arms of the SUNNY trials. However, a plateauing may be more plausible when more active BSC treatments and frequent / multiple surgeries for HS are

considered. For example, the BSC cohort are modelled to have between 24 and 34 surgeries over their lifetime, depending on whether company or EAG BSC transitions are preferred. It would be expected that these surgeries would provide symptom relief, and would have an impact on HiSCR, even if this was not sustained over the longer term. This would lead to fluctuation of response status over multiple model cycles, resulting in a regression to the mean, observed in the plateauing of the response curves over time.

The EAG are concerned that arbitrarily reducing the proportion responding to BSC over time increases uncertainty further. For example, it is unknown what proportion of response might be lost, and over what time point. The EAG acknowledges committee concerns but retains its base case position to prefer the use of 16-week data from the placebo arms of the SUNNY trials for the long-term BSC extrapolation. Several concerns remain regarding the company preference to use PIONEER II data for the BSC transitions:

1) *Imbalances between the studies described in the EAG critique of the company response to technical engagement are not fully alleviated by the company's expert opinion responses. Whilst it is argued that hurley staging and exposure to surgery are unlikely to preclude the use the PIONEER II data, no evidence is provided to support this.*

2) *In the company preferred base case analysis, with the stopping rule applied, and up-titration removed, the response curves imply a RR of response (secukinumab Q4W vs. BSC) of* [redacted] *at 1 and 5 years respectively, despite only* [redacted] *of the cohort being on secukinumab treatment. By contrast, in the EAG preferred base case, the implied RRs are* [redacted] *at 1 and 5 years respectively. The company's preferred modelling assumptions suggest that the treatment effect size for secukinumab grows substantially over time and is likely to be substantially larger than the effect size estimated from the SUNNY trials, with odds ratios for the primary outcome analysis of* [redacted] *and* [redacted] *in the SUNSHINE and SUNRISE studies respectively. Using data provided in Tables 17 and 18 of the original company submission, this approximates to an unadjusted risk ratio of* [redacted] *averaged across the two sunny trials. The company has provided no evidence in support of this continuing increase in treatment effect over time. The EAG's preferred extrapolations imply a more conservative and stable treatment effect size over time that more closely aligns with the clinical*

effectiveness outcomes from the SUNNY trials at week 16. The company and EAG preferred implied treatment effect sizes (i.e. the relative proportion of the cohort in the response states at each time point) are summarised graphically in figure 1 for each model cycle up to cycle 60.

Figure 1 Implied risk ratio for the proportion of the cohort occupying the response states (HiSCR>50) at different time points for the company and EAG preferred analyses.

3) *Regardless of the decision to use PIONEER II or placebo arm data from the SUNNY trials at week 16 to inform BSC transitions, the effectiveness of BSC may still be under-estimated in the model for two reasons: first, the model does not capture the benefit of more active drug treatment as part of BSC that would be used in UK clinical practice. Secondly, it ignores the potential for surgery to provide improvements in HiSCR.*

The EAG and company preferred response curves are summarised in Figures 2 and 3 below.

Figure 2 Response curve traces (EAG preferred base case post ACD, without up-titration)

Figure 3 Response curve traces (Company preferred base case post ACD, without up-titration)

Issue 4: Transition probabilities for the secukinumab arm of the model.

The ACD noted that the committee were concerned that the model output from the EAG and company preferred base case analyses both over-estimated response rates, defined as HiSCR 50 and above, for secukinumab Q4W dose compared to data available from the SUNNY trials at 16- and 52-weeks. The company updated their base case modelling assumptions, applying per cycle transitions for secukinumab and BSC up to week 16 (induction phase) and average cycle transitions up to week 52 (maintenance phase) and extrapolated over the model lifetime horizon whilst on treatment.

The EAG is satisfied that the company's revised approach accurately aligns the transition probabilities over the first four model cycles (induction phase) with the proportion responding at week 16 in the SUNNY trials. The output is demonstrated in Table 6 of the company response to the ACD. The EAG agree with the company that several modelling assumptions, including modelled stopping rules at week 16 and beyond prevent validation of the model base case output against the secukinumab arm of the SUNNY trials at 52 weeks because the SUNNY trials retained patients on secukinumab treatment up to 52 weeks regardless of response.

Issue 5: Treatment specific utility values in the non-response state

The committee accepted the use of treatment specific health state utility values (HSUVs) for the non-response health state, but only up until week 16 in the model. That was because the committee were not satisfied that the treatment specific gain in utility for the non-response state would continue indefinitely. Because of the uncertainty, committee preferred to apply treatment pooled HSUVs beyond week 16 for the remainder of the model time horizon in all health states. In response to the ACD, the company retain their original preference to apply treatment specific HSUVs in the non-response state for the full model time horizon. They highlight clinical evidence supporting their case provided during technical engagement at the EAG request and have provided additional clinical data to support an assumption of a continuing benefit of secukinumab in the non-response state using data collected at 52 weeks.

The EAG agree with the company that the use of treatment specific HSUVs in the non-response state is justified and supported by the available clinical data, including the

additional supporting evidence provided in response to the ACD. The EAG would particularly draw the committee's attention to Tables 18 and 19 of the company response which show that there is no evidence of secukinumab utilities reducing in the secukinumab non-response state between week 16 and 52. Given the SUNNY trial design, comparable data are not available for the placebo arm meaning a direct comparison was not possible, but the EAG are satisfied that there is no evidence to suggest that the utility for secukinumab would reduce over time, other than through usual utility reductions due to increasing age.

The EAG also note that applying treatment specific HSUVs only up to week 16 requires an assumption that BSC patients increase their utility arbitrarily at week 16, whilst secukinumab patients reduce their utility arbitrarily at week 16, despite remaining in the non-response state. The EAG does not consider this to be the preferred approach as there is no evidence to support such changes in utility within state. The EAG therefore considers it more plausible to apply treatment specific utility values in the non-response state for the full model time horizon, reflecting that non-responders who remain on treatment may continue to get some clinical benefit from secukinumab. Given that a stopping rule is now applied, the risk of consistent non-responders getting a utility gain in the non-response state is also minimized as such patients now transition to BSC in the model.

Issue 6: BSC costs

The company base case post ACD is aligned with committee and EAG preferences. BSC treatment acquisition costs are informed by the treatments allowed within the placebo arms of the SUNNY trials. Surgery costs are retained within the model.

The EAG are satisfied that the company, committee and EAG preferences for BSC costs are now aligned and consider the issue to be resolved.

Issue 7: Surgery costs

Given uncertainty surrounding HS surgery costs, the committee preferred the EAG's more conservative weighed average surgery cost (£1,217). The company retain their preference to align costs with those included in TA392 (£2,402). The company sought additional blinded clinical expert opinion regarding company and EAG preferred surgery costing approaches.

Whilst the experts more closely aligned with the company approach, they highlighted substantial uncertainty, including noting that many procedures are completed as day case and may be classed as intermediate and minor procedures to provide symptomatic relief.

The EAG maintains its preference to apply weighed average surgery costs of £1,217, accounting for a mix of minor, intermediate, and major procedures (see details in EAG critique of company response to technical engagement). The EAG preferred costs reflect the discussion at the committee meeting, where it was acknowledged that most surgeries are minor, and many can be completed as day case procedures. The EAG approach to costing applies a weighted average cost, based on finished consultant episodes reported in hospital episode statistics. The EAG is not aware of any concerns that the weighting of setting and classification of surgery within these HRG codes does not reflect the resource use for HS surgery. The EAG acknowledges the company's arguments around inflation but does not consider them relevant as the underlying assumptions about surgery type and setting are different to those used in TA392. The company's preferred approach assumes that there are no minor procedures, though they provide a scenario where some minor procedures are included. The proportion of minor procedures however is not evidence based, and the base case assumption is inconsistent with the advice received by the EAG's clinical expert, the advice provided by clinical experts at the first committee meeting and appears inconsistent with the advice provided from the company's clinical experts. The EAG preference therefore remains unchanged and remains aligned with the committee's preference.

Issue 8: Hospital resource use rates

Committee, company and EAG preferences are now aligned.

Despite uncertainty in resource use data, the EAG considers this issue to be resolved.

Issue 9: Outpatient resource use rates

The committee preferred the EAG proposed outpatient resource use rates to avoid the risk of double counting. However, the company has provided further re-assurance that outpatient resource use was not double counted, including full details of the exact questions posed to clinical experts consulted by AbbVie for TA392.

The EAG has reviewed the exact questionnaire wording provided by the company. Whilst the wording of the questions is not completely unambiguous and does not completely rule out the risk of double counting, the EAG is satisfied that the risk of double counting is low. Despite broader concerns about uncertainty surrounding resource use raised in the EAG report, the impact of uncertainty surrounding the number of outpatient resource use visits on the ICER is minimal. The EAG are therefore satisfied that the company's additional clarification is sufficient to allow us to accept the company's preferred outpatient resource use estimates.

Results:

Table 2: Summary of analyses resulting from changes to the company preferred base case to align with NICE preferred base case assumptions.

Sc.	Scenario	Incremental Costs	Incremental QALYs	ICER
Co. BC	**Company preferred base case post technical engagement**	[redacted]	[redacted]	**£42,415**
1	Alignment of BSC (drug acquisition) costs with placebo arm of SUNNY trials.	[redacted]	[redacted]	£45,091
2	Inclusion of stopping rules at week 16 and for sustained (3 cycles) non-response thereafter.	[redacted]	[redacted]	£51,945
3	Use of 4-weekly cycle specific transitions for the induction phase of the model	[redacted]	[redacted]	£42,447
4A	**Company revised deterministic base case analysis post ACD (1+2+3)**	[redacted]	[redacted]	**£54,554**
4B	**Company revised probabilistic base case analysis post ACD**	[redacted]	[redacted]	**£54,282**

Abbreviations: ACD: appraisal consultation document; BSC: Best supportive care; Co. BC: company base case analysis; EAG: external assessment group; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year

Table 3: Summary of the impact of EAG preferred assumptions applied to the company preferred base case post ACD.

Sc.	Scenario	Incremental Costs	Incremental QALYs	ICER
Co. BC	**Company revised deterministic base case analysis post ACD**	[redacted]	[redacted]	**£54,554**
1	Removal of up-titration	[redacted]	[redacted]	£61,508
2	BSC transitions based on placebo arm of SUNNY trials	[redacted]	[redacted]	£97,210
3	Use of EAG preferred surgery costs	[redacted]	[redacted]	£57,876
4A	**EAG preferred <u>deterministic</u> base case analysis post ACD**	[redacted]	[redacted]	**£105,353**
4B	**EAG preferred <u>probabilistic</u> base case analysis post ACD**	[redacted]	[redacted]	**£105,667**

Abbreviations: ACD: appraisal consultation document; BSC: best supportive care; Co. BC: company base case analysis; EAG: external assessment group; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year

Table 4: Additional scenario analyses applied to EAG base case to align with committee preferred assumptions.

Sc.	Scenario	Incremental Costs	Incremental QALYs	ICER
EAG. BC	**EAG preferred <u>deterministic</u> base case analysis post ACD**	[redacted]	[redacted]	**£105,353**
1	Use of treatment specific utility values for the non-responder state for induction phase only.	[redacted]	[redacted]	£140,605
2	Outpatient resource use as per EAG preference at TE	[redacted]	[redacted]	£106,111
3A	**<u>Deterministic</u> base case analysis aligned with ACD preferences (EAG BSC transitions)**	[redacted]	[redacted]	**£141,616**
3B	**<u>Probabilistic</u> base case analysis aligned with ACD preferences (EAG BSC transitions)**	[redacted]	[redacted]	**£141,386**
4A	**<u>Deterministic</u> base case analysis aligned with ACD preferences (Company BSC transitions)**	[redacted]	[redacted]	**£87,515**
4B	**<u>Probabilistic</u> base case analysis aligned with ACD preferences (Company BSC transitions)**	[redacted]	[redacted]	**£87,098**

Abbreviations: ACD: appraisal consultation document; BSC: best supportive care; Co. BC: company base case analysis; EAG: external assessment group; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year

Figure 4 ***Company preferred scatter plot of probabilistic runs on the cost-effectiveness plane.***

Figure 5 ***Company preferred cost-effectiveness acceptability curve.***

Figure 6 EAG preferred scatter plot of probabilistic runs on the cost-effectiveness plane.

Figure 7 EAG preferred cost-effectiveness acceptability curve.

Summary

The EAG has reviewed the company response to the ACD. All changes made to the economic model post ACD have been fully described in the company response document and the EAG is satisfied that all amendments to the model have been appropriately implemented. The EAG consider there to be two main areas of residual uncertainty that have major impacts on the cost-effectiveness results. These are uncertainty surrounding the most appropriate source of data for BSC transition probabilities and whether to apply treatment specific health state utility values in the non-response health state over 16 weeks or over the full model time horizon. Both of these issues have substantial impact on the ICER. The EAG note that, at the current modelled price, the ICER for secukinumab is substantially higher than £20,000 to £30,000 per QALY under both the company and EAG preferred assumptions.