Evidence Review Group's Report

Title: Guselkumab for treating moderate to severe plaque psoriasis

Produced by *Warwick Evidence*

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Paul Sutcliffe (Associate Professor) coordinated the project. Ewen Cummins (Health Economist) conducted, reviewed and critiqued the cost-effectiveness evidence. Chidozie Nduka (Research Fellow) coordinated and conducted the critique of clinical effectiveness evidence. Martin Connock (Senior Research Fellow) and Daniel Gallacher (Research Associate) conducted the critique of clinical effectiveness and critique of statistical analysis. Pam Royle (Information Specialist) conducted the critique of the company searches and conducted ERG searches. Aileen Clarke (Professor) and Amy Grove (Assistant Professor) commented on draft versions of the report and formatting of the report. All authors contributed to the writing and formatting of the report.

Glossary of terms

AE	Adverse Events
Anti-IL	Anti-interleukin
Anti-TNF	Anti-tumour necrosis factor
BADBIR	British Association of Dermatologists Biologic Interventions Register
ERG	Evidence Review Group
FTA	Fast Track Appraisal
MOA	Mechanism of Action
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
PAS	Patient Access Scheme
PASI	The Psoriasis Area and Severity Index
RCT	Randomised Controlled Trial
SAE	Serious Adverse Events
STA	Single Technology Appraisal
WDAE	Withdrawal Due to Adverse Event
QALY	Quality Adjusted Life Year

1. Summary of the ERG's view of the company's FTA case

The technology is not pharmacologically similar to the comparators

Guselkumab is an anti-IL agent of a particular type; namely an anti-IL-23 drug. According to ERG's clinical advice there are four classes of anti-IL agent (anti-IL-23, anti-IL-23/12, anti-IL-17, and anti-IL-17-receptor agents), each with a particular mode of action operating to influence the generation of IL-17.[1-3] IL-17 has been identified as a powerful mediator of psoriatic inflammation.[4]

One of the comparators selected by the company was ustekinumab, an anti-IL-23/anti-IL-12 agent. This has a differing mechanism of action (MOA) to guselkumab, as agreed by the company (Janssen) in their submission (CS; Box B of Document B, page 29, Document A page 18), and reinforced by the results of the NAVIGATE trial.[5] The company's second comparator was adalimumab, an anti-TNF agent with different pharmacology to guselkumab. In short, although both selected comparators differ pharmacologically from guselkumab, ustekinumab is more similar as it is also an anti-IL agent.

The selected comparators are appropriate

This technology appraisal has been submitted during a period of rapid change in the range of interventions recently approved or under consideration by NICE for treating moderate to severe plaque psoriasis, including ustekinumab (TA180), ixekizumab (TA442), secukinumab (TA350), and tildrakizumab (ID1060).

Overall, the ERG agrees that the comparator treatments used in the company submission (CS) meet the criteria set by NICE. According to the NICE criterion of "*significant market share*" the choice of ustekinumab and adalimumab as comparators appears justified. However, in response to the ERG's clarification questions, the company supplied details of current market-share data (2014 to 2017)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The ERG considers that emerging treatments such as ixekizumab and secukinumab could provide optimal comparators for cost comparison. It is of note that both adalimumab and ustekinumab are clinically less effective than ixekizumab, at least in the short term, as demonstrated in the company's network meta-analysis (NMA) for adalimumab, and in short follow up RCTs [6, 7]for ustekinumab. Longer term real-world data on effectiveness and safety is lacking for the newer anti-IL agents (guselkumab, ixekizumab, secukinumab).

With reference to the "FTA-Guiding notes for ERGs v2" provided by NETSCC, which indicates that the selected comparator should "*adequately represent the NICE recommended treatments as a whole, both in terms of its cost and effects"*, the ERG considers that ustekinumab may not be representative of recommended anti-IL agents in terms either of pharmacology or effectiveness, while subcutaneously administered anti-TNF agents such as adalimumab have been shown to be inferior to anti-IL agents in several trials (Clarification Document Table 6; CS Document B, Appendices Table 8).

Strength of the case for undertaking an FTA

Evidence indicates that there is a low risk that guselkumab is less effective than other available biologicals for moderate to severe psoriasis including those recommended by NICE. The strength of the company's case for undertaking an FTA appeared to depend on the cost comparison modelling, and in the appropriateness of comparator choice.

2 Critique of the decision problem in the company's submission

The decision problem assesses the use of the anti-IL 23 agent guselkumab in the treatment of patients with moderate to severe plaque psoriasis who are candidates for systemic therapy, consistent with the recent positive CHMP by the EMA.

The CS decision problem meets the NICE scope for this intervention and the different outcomes. While addressing the NICE scope for the population, the company further characterises the target population for guselkumab as patients with moderate or severe

psoriasis whose symptoms are refractory or contraindicated to non-biologic systemic treatments or phototherapy. The ERG agrees that this population is relevant to clinical practice. However, the ERG notes that patients naïve to prior systemic non-biologic treatment or prior phototherapy – comprising more than a third of the study populations in the VOYAGE trials[8, 9] – do not meet the company's decision problem. In their decision problem, the company also included several systemic biologic treatments as comparators, but excluded systemic non-biologic treatments and phototherapy. While this means that the decision problem only partially meets the NICE scope for the comparators, the ERG agrees with the company's rationale that guselkumab will only be substituted for existing systemic biologic treatments, and not for any of the non-systemic biologic agents or phototherapy. More so, the NICE technical team advised that cost comparisons of guselkumab be made only against alternative biologic agents (ustekinumab and adalimumab). The company's decision problem includes two of the three subgroups stated in the NICE scope (previous use of systemic and of non-systemic biologic treatments): subgroup analysis by psoriasis severity was not performed.

3 Summary of the ERG's critique of clinical effectiveness evidence submitted

3.1 The submission

The submission comprised: A summary document (A) of 36 pages; an Evidence Submission document (B) of 123 pages, and an Appendices document (172 pages) for Document B. Janssen supplied further analyses and evidence in a clarification document of 92 pages.

Three randomised multicentre controlled trials, VOYAGE 1, VOYAGE 2, and NAVIGATE, informed the clinical effectiveness evidence submitted by the company.

VOYAGE 1 investigated the efficacy of guselkumab, compared to adalimumab (and placebo) for the treatment of patients aged ≥ 18 years with moderate to severe plaque psoriasis for at least 6 months; 837 patients from 101 sites in 10 countries (CS; Table 7, Document B) were randomised 2:2:1 to guselkumab (n = 329), adalimumab (n = 334), or placebo (n = 174). Mean age was 43.7 years; 72.6% were male, mean duration of was 17.5 years, and 20.9% had received prior systemic biologic treatment. Administration schedules are summarised in Figure 2 (CS; page 35, Document B). The injection schedule was arranged to achieve double blind status for patients and physicians.

VOYAGE 2[8] was conducted simultaneously with and was similar to VOYAGE 1[9]: guselkumab was compared to adalimumab (and placebo). There were 115 centres in nine countries; patient details were very similar to VOYAGE 1 (CS; Table 7, Document B). NAVIGATE investigated the efficacy of guselkumab in moderate-to-severe plaque psoriasis refractory to ustekinumab at 100 sites in 10 countries (CS; Table 7, Document B). 871 patients initially received open-label ustekinumab at licensed dosage at 0 and 4 weeks (CS; Table 9, page 52, Document B). At 16 weeks, 30.8% (n= 268) of patients had inadequate response and were randomised to a standard schedule of guselkumab (CS; Figure 4, Document B) or to continue ustekinumab at week 16 and every 12 weeks thereafter through week 40 with placebo injections to maintain blinding. Among patients randomised at 16 weeks average age was about 44 years, 68% were male and the mean duration of psoriasis was 16.9 years. Only patients randomised at 16 weeks were included in the main analyses. CS; Tables 10, 12 and 13 of document B summarise the key efficacy and safety outcomes of the three trials. At 16 weeks guselkumab PASI 75 response rates were significantly higher (~90%) than for adalimumab (~70%) or placebo (~5.7%); with PASI 90 as the measure of efficacy similarly superior response rates were found for guselkumab (~80% versus ~50% for adalimumab). Post-randomisation PASI 90 response rates obtained on **more than** two visits were also higher for guselkumab (54.1%) compared to the ustekinumab (23.3%) in the NAVIGATE trial (CS; Table 13, Document B).

Subgroup analyses of PASI 90 at week 16 revealed that guselkumab was consistently better than placebo in VOYAGE 1 (CS; appendix E, Figures 63-65) and VOYAGE 2 trials (CS; Appendix E, Figures 69-71). No subgroup analyses were presented for NAVIGATE, despite the company reportedly planning to do so (CS; Table 7, Document B).

The company performed a series of network meta-analyses (NMAs) involving 45 randomised controlled trials, to ascertain the efficacy of guselkumab compared indirectly to other systemic biological treatments for moderate and severe psoriasis. Together with the NMAs provided during clarification altogether approximately 27 NMAs were presented. Pairwise comparisons with guselkumab adjusted for placebo response rates (described by the company as “baseline risk-adjusted”) from the NMAs were summarised in CS; Table 14 of document B and CS; Table 4 Document A. Guselkumab had superior efficacy to other systemic biological agents except ixekizumab. Adjusted NMA analyses (CS; Table 4 Document A) for PASI 75 indicate statistically significant superiority of guselkumab over subcutaneous

biologicals other than ixekizumab which was equally effective (RR = 1.0). PASI 90 response rate for guselkumab was comparable to ixekizumab (RR 1.00, 95% CrI 0.88 to 1.12), but superior to the other treatments. Similarly, PASI 100 response rates for guselkumab were comparable to ixekizumab and infliximab, but significantly superior to other comparators.

3.2 ERG's critique of clinical effectiveness evidence submitted

The ERG considered the eligibility criteria applied in the selection of evidence for clinical effectiveness. Although the ERG could not appraise the studies excluded from the review as no detail was presented in the CS, the ERG believe the eligibility criteria to be reasonable and consistent with the decision problem outlined in the final NICE scope. Searches in the company submission (CS; Document B Appendices Tables 1, 2 & 3) were conducted in February 2017, updated in August 2017, and yielded the VOYAGE 1, VOYAGE 2, and NAVIGATE trials. The ERG considers the searches for clinical effectiveness evidence to be adequate and believe that the included RCTs of guselkumab are relevant to the decision problem and no relevant published trials were excluded.

We consider that the findings from the VOYAGE trials may reflect favourably on guselkumab through the selection of adalimumab as comparator. Previous technology appraisals (e.g. TA350 secukinumab and TA419 ixekizumab) have ranked the efficacies of TNF-α inhibitors (such as adalimumab) lower than anti-interleukin agents for this indication and these have already been compared head to head with an alternative anti-IL agent (ustekinumab).[8, 9] The submission mentions an ongoing trial to compare guselkumab versus secukinumab (ECLIPSE), but no results are yet in the public domain. Analyses of the primary endpoint (PASI 90 at 16 weeks) revealed that guselkumab was consistently superior to placebo across different population subgroups (CS; Figures 62 – 64 and 68 – 70 of document B Appendix E), however the CS does not present any subgroup analyses of guselkumab compared to adalimumab at 16 weeks. The company has instead presented subgroup efficacy analyses at 24 weeks. While the findings mostly show guselkumab superior to adalimumab, the ERG cannot ascertain that guselkumab will be superior to adalimumab in all subgroups at 16 weeks.

The ERG has concerns over the relevance of reporting PASI 90 at trial visits in the NAVIGATE trial within the CS (Table 13, Document B) and considers that the PASI 90 response rate at 28 weeks may have been a more appropriate study endpoint

response rate at 28 weeks reported in the published (NAVIGATE) article to be a more appropriate study endpoint.[5]

The company performed a series of 'full' NMAs which compared guselkumab to all possible systemic biological psoriasis treatments, including treatments not licensed for treating plaque psoriasis in the UK (CS; Figures 19 – 39, Document B Appendix D), and additionally performed sensitivity analyses restricting the NMAs to only comparators specified in the decision problem (CS; Table 8 and Figures 11 – 29, Clarification Document). The ERG consider the latter (or restricted) NMAs to be more appropriate and consistent with the final scope. However, the 'restricted' NMA comprised treatment doses that were unlicensed in the UK for the treatment of plaque psoriasis (e.g. secukinumab 150 mg), hence it is not clear to the ERG what the inclusion criteria were for this restricted set. Although the company maintains in their clarification response that the restricted NMA comprised only comparators specified in the decision problem, the ERG still queries the inclusions of secukinumab 150mg in the network (CS; Table 9, Clarification Document). Nonetheless, the 'full' and 'restricted' NMAs provide somewhat similar interpretations of the results. Although the Surface Under the Cumulative Ranking (SUCRA) curves were only provided for the 'full' NMA (CS; Figure 50, Document B Appendix D), the ERG believe that the SUCRA curves for the restricted network would be consistent with those for the 'full' NMA. The studies included in the NMA are consistent with the scope of this FTA and there were no baseline differences across populations of the VOYAGE trials and comparator RCTs. Although there are some differences between the ERG and the company (CS; Table 15, Appendix D) in assessment of the quality of the included studies, the ERG consider that the quality of the included RCTs was assessed using well-established and recognised criteria and that the methodological quality of the VOYAGE and NAVIGATE trials and comparator RCTs was reasonable overall.

The ERG did not have the opportunity to reproduce the NMA presented by the company and could only validate through a review of the presented input, output and WinBUGS code. The ERG verified the baseline and outcome data extracted from each trial in the NMA, as reported in CS; Document B Appendices Tables 7 and 8, respectively. Overall, the level of accuracy was high with most discrepancies expected to have minimal impact on the NMA. A few larger inconsistences in the extracted data were found (see safety evidence below), however the ERG cannot tell if these errors are confined to the tables, or if they were carried

into the NMA. The ERG also found slight inconsistency in the selection of results used in the NMA when studies reported results based on both last observation carried forward (LOCF) and non-responder imputation (NRI) methods for coping with missing data, with no clearly defined rule provided by the company. However, any impact of this on the NMA is thought to be minimal.

The ERG were concerned that any categorisation of a continuous outcome such as the DLQI score may discard valuable data and increase the chance of a significantly positive association being falsely positive. The company's reproduction of the NMA using change in mean DLQI conducted at the ERG's request, found no difference in interpretation (CS; Figures 4 – 7, Clarification Document).

Statistical homogeneity in the NMA was not formally considered in the CS and the similarity assumption was not satisfied. However, the company presents a number of adjusted NMAs (CS; Tables 12 & 13, Document B Appendix D) which attempt to account for dissimilarity as well as clinical and methodological heterogeneity. Nonetheless, the ERG also notes there are studies that have not reported the covariate of interest for each possible adjustment and it is not clear how these were managed. On further clarification, the ERG consider that the consistency assumption was met using the deviance information criteria (CS; Tables 7 & 8, Clarification Document). The random effects model had the best fit for all pairwise analyses in the NMA, hence all results presented were from this model. No subgroup analysis was performed. Overall, the methodological quality of the NMA was good and the ERG found the results to be broadly consistent with previous NICE technological appraisals.

3.3 ERG's critique of safety evidence submitted

The company presented summaries of key safety events from the three trials (CS; Tables 15-21 Document B). In general, there were no major differences between guselkumab and the comparator drugs.

During the first 16 weeks of the VOYAGE trials, AE frequency was similar between placebo, guselkumab and adalimumab. The 16-48 week follow-up period of VOYAGE 1 also showed close similarity between guselkumab and adalimumab. The types and frequencies of AEs were generally similar in all trial arms, the most common of which was nasopharyngitis

(6.5%-10.5%). However upper respiratory tract Infections (URTI) were more common for guselkumab than adalimumab across both VOYAGE trials at all reported outcomes.
The design of NAVIGATE made a direct safety comparison between ustekinumab and guselkumab over weeks 16-40 and weeks 16-60 of the trial, a period over which patients received two induction and two (weeks 16-40) or three (weeks 16-60) maintenance doses of guselkumab. The ERG requested detailed information on AEs from NAVIGATE for weeks 16-32 as a clarification, however the company provided the information for the period of 16-40 weeks in their response.

Whilst this information should be interpreted with caution due to the treatment crossover and longer duration of treatment, the overall experience of AEs for guselkumab in NAVIGATE (54.1%) was comparable to that of guselkumab patients from VOYAGE 1 (51.7%) and 2 (47.6%).

The clarification (CS; Table 16 Clarification Document) revealed that, for the randomised period of NAVIGATE, the following adverse events affected more people on guselkumab than on ustekinumab: infections and infestations (31.1% v 21.8%); general disorders and administration site conditions (10.4% v 2.3%); musculoskeletal and connective tissue disorders (10.4% v 5.3%). For the same period, guselkumab reported more patients who experienced AEs (54.1% v 46.6%), with both more cases of nasopharyngitis (13.3% v 9.8%) and URTI (7.4% v 3.8%). Whilst these events are mostly minor in severity, there is a consistent pattern suggesting a slightly inferior safety profile for guselkumab compared to ustekinumab in patients previously treated with ustekinumab.

Reported serious adverse events (SAE) were comparable between adalimumab and guselkumab, however a higher frequency was observed in guselkumab patients (3.7%) than in ustekinumab patients (1.5%) in weeks 16-40 of NAVIGATE, with a similar difference observed at 60 weeks.

Discontinuation due to AEs was similar between comparators across each of the three trials at every reported time-point.

The company performed safety NMAs, both on their full and restricted networks, using AEs, SAEs and withdrawal due to AEs as outcomes. Initially only pairwise results were presented

for the restricted NMA (CS; Table 14 Document B), however upon request, full results were submitted in clarification.

The results (CS; Table 14 Document B & CS Clarification Document Figure 25, 27, and 29) – indicate there were no statistically significant differences between guselkumab and other subcutaneous biological treatments across any of the safety measures (AE, SAE WDAE), suggesting that guselkumab is no less safe than other (subcutaneous) systemic biologic agents.

The ERG compared the reported safety outcomes to the published trial reports and noted that consistency was high. The observed inconsistences are tabulated in Appendix 1 of this report. No information from any of the three trials was provided on infrequent AEs that may be specific to a particular treatment or be associated with higher maintenance costs.
The input to the NMA was assumed to match the figures reported in Table 8 of the CS Appendix document, which was checked by the ERG for reliability to the published study reports. Overall accuracy was high. The most significant errors are reported in Appendix 1 of this report.

4 Summary of the ERG's critique of cost evidence submitted

4.1 Company cost comparison

The company presents the [redacted] costs of treatment for all the biologics currently approved by NICE in CS; Table 22 of Document B. This does not take into account the secukinumab and ixekizumab PASs.

On the basis of market share data, as reviewed later in this document, the company presents the formal cost comparison of guselkumab against adalimumab and ustekinumab. It is assumed that all treatments have the same [redacted] PASI75 response rate as estimated for guselkumab within the company NMA. PASI75 responders go on to receive maintenance therapy, having a 20% annual discontinuation rate thereafter.

The company states that 5 years is sufficient to capture the majority of the costs of guselkumab, with around 30% of patients remaining on treatment at the end of the 5 years. The undiscounted [redacted] costs, inclusive of the guselkumab PAS, are [redacted] for guselkumab, £25,785 for adalimumab and £27,928 for ustekinumab. Guselkumab is

[redacted] than adalimumab by [redacted] and is [redacted] than ustekinumab by [redacted].

The company presents a range of one-way sensitivity analyses in CS; Table 27 of Document B which broadly maintain the above conclusions.

Previous assessments of the biologics

Table 1: Timing of previous STAs and NICE recommendations

	Treatment	FAD	Group	PASI	DLQI	Induction	Continuation
TA103	Etanercept	08/2005	Severe	≥ 10	> 10	12 wk	PASI75, or PASI50 and DLQI 5pt fall
TA146	Adalimumab	04/2008				16 wk	
TA180	Ustekinumab	08/2009				16 wk	
TA350	Secukinumab*	05/2015				12 wk	
TA442	Ixekizumab*	03/2017				12 wk	
TA134	Infliximab	11/2007	V.Severe	≥ 20	> 18	10 wk	
* And the company provides the treatment with the agreed patient access scheme (PAS)							

Infliximab is only approved for very severe psoriasis and also requires IV administration, the ERG has therefore not considered it further in the economics.

As far as the ERG can ascertain, while there has been some minor variation in list prices over time the drug costs are essentially the same across the assessments including the current assessment. The exception to this is etanercept for which there is now a generic which is 8% cheaper than the branded item.

Etanercept was approved through an MTA. Within the formal cost effectiveness estimates presented, for the cost effectiveness of etanercept to fall within conventional NICE thresholds required the assumption that patients not responding to therapy would be hospitalised for 21 days each year[1], probably also coupled with the quality of life values of those with more severe disease[2] being applied.

[1] Tables 6.3.1, 6.3.4, 6.3.7 and 6.3.10 of the AG report
[2] 4th quartile of the DLQI distribution at baseline as presented in the table of the next subsection.

It appears that the Fonia et al (2010)[11] costings were first applied during the STA of secukinumab. These costings suggest fewer annual inpatient days per patient and imply that the inpatient cost offset from a response is somewhat less than that assumed during the etanercept assessment. It is possible that some or all of the biologics are not cost effective compared to best supportive care at conventional NICE thresholds. If so, a formal cost effectiveness analysis might, other things being equal, estimate the biologic which has a lower PASI75 to be more cost effective than a biologic with a higher PASI75.

The approval of secukinumab was conditional upon a PAS. The AC concluded that: "*the most plausible assumptions on resource use were closer to Fonia et al. than to NICE's psoriasis guideline*", "*the ICERs compared with the biological treatments rather than with best supportive care were most appropriate*", "*using direct trial data, secukinumab was more effective than at least one of the already recommended biologicals, etanercept*" and given "*the clinical data (compared with etanercept in the FIXTURE trial and with the results of the network meta-analysis), and the testimony of the experts… the most plausible ICER was likely to be in line with the other biologicals already recommended in previous NICE guidance*".

The approval of ixekizumab was conditional upon a PAS. The AC concluded that, "*the most plausible ICER was likely to be in line with the other biological treatments already recommended in previous NICE guidance*".

Market share and comparators

At clarification (CS; Clarification Response to question B1) the company has both updated and supplied more detail about the Quintiles IMS market share data. The company reported that invitations to participate are sent to "*the universe of prescribing doctors*" (Clarification Response, page 84). These are selected on the basis that they have to spend at least 50% of their time in the NHS, have treated at least 6 psoriasis patients with a biologic in the last 3 months, be actively involved in the initiation or switching of treatments and have practised for between 3 and 5 years. The dermatologists were asked to report on moderate to severe psoriasis patients who were treated with a biologic.

[redacted]

[redacted]

[redacted]

During the teleconference with NICE it was stated that reasonable market share related to the absolute market share and that the comparator(s) should be treatments likely to be displaced by guselkumab.

[redacted]

The changes in market shares may be a better indication of what new patients and patients switching treatment are receiving, and so what [redacted]. Adalimumab has a [redacted] market share so seems [redacted]. As the company notes, [redacted].

[redacted]

Since the company has already included adalimumab in the cost comparison there seems little harm in the cost comparison encompassing all the subcutaneous biologics approved by NICE[3], though both

[redacted]. Ixekizumab may be of [redacted] but may be relevant from a cost effectiveness viewpoint since it was approved after secukinumab so might help indicate what could happen if guselkumab was judged unsuitable for an FTA and was sent down the STA route.

During the decision problem teleconference the company outlined that it could not consider ixekizumab, and by implication secukinumab, due to it being ignorant of competitor PASs. These have been supplied to the ERG and are included in the confidential cPAS Appendix.

Cost comparison: Clinical effectiveness

The company cost comparison assumes clinical similarity in terms of PASI75 and discontinuation rates.

Most of the PASI75 relative risk estimates of the company NMA are statistically significant (CS; Table 4 Document A & Table 14 Document B) and it does not seem reasonable to assume clinical similarity. But the relative risks that are statistically significant estimate guselkumab to be superior to the other treatments. There is an argument for a "what if" these treatments were as good as guselkumab – would they be more or less costly than it? But this can largely be assessed simply by examining the annual drug costs. It seems more reasonable

[3] Note that the ERG has had difficulty saving the company cost comparison model workbook once it has been amended by the ERG. As a consequence, the ERG has copied the structure and formulae of the company cost comparison workbook into a new workbook before amending and saving this.

for the cost comparison to apply the central NMA estimates, most of which are statistically significant. Consequently, the ERG will present estimates (a) along the lines of the company similarity assumption and (b) that apply the central NMA estimates.

In considering the relative risk of outcome in the trials within the NMA, it may not be appropriate to assume similarity for the PASI75 estimates, which are not statistically significant; e.g., those for ixekizumab, the central estimates favour ixekizumab over guselkumab.

Previous STAs for psoriasis have in their base cases assumed a common 20% discontinuation rate. This has been augmented in at least one STA by a sensitivity analysis that differentiates these by the rates estimated in Arnold et al (2016).[12]

In the opinion of the ERG and as reviewed in greater detail in Appendix 2, the analyses of the UK BADBIR registry data by Warren et al (2015)[13] and Iskander et al (2017)[14] are better UK sources and suggest annual discontinuation rates of perhaps 9%[4] for ustekinumab, 18% for adalimumab and 29% for etanercept.

The above UK data suggests greater differentiation of discontinuation rates than that of the recent systematic review of No et al[15] which suggests annual discontinuation rate rates of 14% for ustekinumab, 11% for adalimumab and 15% for etanercept.

The above papers do not consider secukinumab. Egeberg et al (2017)[16] analyse Danish DERMBIO registry data and conclude that secukinumab has a worse discontinuation rate than ustekinumab, adalimumab and etanercept. To the ERG the Kaplan Meier plots of the main paper might suggest secukinumab has a similar discontinuation rate as etanercept. The supplementary on-line documentation suggests in-label dosing of secukinumab has a discontinuation rate between those of etanercept and adalimumab. But the estimates for secukinumab may be biased due to the secukinumab patient group having high proportions of patients with experience of 3 prior (18%) and 4+ prior (20%) biologics. One further real world study[17] remarked that fewer patients treated with secukinumab maintained a PASI

[4] Taken to be the simple average of the 7% for 1st line use of Warren et al and the 11% for 2nd line use of Iskander et al.

75 response than was seen in RCTs (FIXTURE, ERASURE, & SCULPTURE). For the sensitivity analyses around discontinuation rates the ERG will assume secukinumab has the same discontinuation rate as etanercept but this may not be realistic.

It may be more reasonable to disregard differential discontinuation rates for the comparisons between the interleukin inhibitors and to consider these as a class with a common annual discontinuation rate of the 9% BADBIR estimate for ustekinumab. In the absence of other data, the ERG will simply assume that ixekizumab and guselkumab have the same discontinuation rate as ustekinumab.

Considerations if guselkumab were to proceed to an STA

Ixekizumab is the most recently approved subcutaneous biologic so may be the most informative in terms of how guselkumab might be assessed within an STA if it is judged unsuitable for an FTA.

The company NMA estimates of CS Table 14 of Document B suggest minimal difference between guselkumab and ixekizumab at central estimates for PASI75 with a relative risk of 0.98 (0.93-1.02) in favour of ixekizumab. This eases matters for costing purposes since roughly similar [redacted] of patients will be modelled as receiving guselkumab maintenance therapy as ixekizumab maintenance therapy.

The NMA also suggests no difference in PASI90 with a relative risk of 1.00 (0.88-1.12). If there is any difference it may lie in the PASI100 with a relative risk of 0.90 (0.74-1.08) in favour of ixekizumab.

The company submission of TA442[5] provides the ixekizumab trials' EQ-5D-5L quality of life values among patients with a baseline DLQI > 10, not adjusted for baseline characteristics. Sensitivity analyses using the all patient EQ-5D-5L adjusted for baseline characteristics and the EQ-5D-PSO[6] among patients with a baseline DLQI > 10 are also

[5] Table 114

[6] The ED-5D-5L with 2 additional psoriasis dimension bolt-ons valued using the UK TTO estimates of Swinburn et al. Development of a disease-specific version of the EQ-5D-5L for use in patients suffering from psoriasis: lessons learned from a feasibility study in the UK. *Value Health* 2013;**16**:1156-62.

presented. These are the only quality of life estimates that the ERG is aware of[7] that differentiate PASI90 from PASI100. This permits a crude comparison as below.

Table 3: Response rates at central estimates[8] and quality of life values

	PASI response at induction			
	<75[9]	75-89	90-99	100
All patients				
Guselkumab	16.5%	10.4%	45.0%	28.1%
Ixekizumab	14.8%	12.1%	41.8%	31.2%
TA103 QoL values:				
Δ EQ-5D-3L: DLQI 4th quartile	+ 0.20	+ 0.38	+ 0.41	
TA442 QoL values				
Δ EQ-5D-5L: DLQI > 10	+ 0.062	+ 0.130	+ 0.139	+ 0.141
Δ EQ-5D-5L: All patients	+ 0.038	+ 0.083	+ 0.102	+ 0.104
Δ EQ-5D-5L-PSO: DLQI > 10	+ 0.069	+ 0.141	+ 0.148	+ 0.198

At central estimates those without a PASI75 response differ by only around 2%. These patients would only remain on treatment during induction and so any QALY difference from this source is likely to be minimal. The flip side of this is that around 2% more patients fall into the PASI75-89 category for ixekizumab and will receive ongoing maintenance therapy and the quality of life increment.

Given the unitary relative risk for PASI90 the proportion of patients with PASI90 is the same for guselkumab and ixekizumab. These are split between PASI90-99 and PASI100 based upon the 0.90 relative risk for PASI100. This causes ixekizumab to have around 3% more in PASI100 and 3% less in PASI90-99 compared to guselkumab. Whether there would be any QALY gain from ixekizumab over guselkumab at central estimates depends upon which set of quality of life values is most credible, coupled with any differences in discontinuation rates among responders. Only the TA442 EQ-5D-5L-PSO among those with a baseline DLQI > 10 suggests much difference in the quality of life gain between a PASI 90-99 and a PASI 100 response: 0.05.

[7] The ERG has not undertaken a formal review of quality of life values.
[8] The company has supplied estimates for placebo PASI75 of 5.1%, PASI90 of 1.69% and PASI100 0.44%.
[9] Taken to be the mean of PASI<50 and PASI50-74

In short, the differences in the patient distributions at central NMA estimates are small. The long term QALY differences if formally modelled are likely to be correspondingly small. It seems likely that the AC of an STA of guselkumab would for the comparison with ixekizumab concentrate upon the differences in costs. Given the very similar PASI75 rates it is likely that these differences would be driven by the [redacted] costs as presented in this document and its cPAS appendix.

Drug cost calculations: CS Table 22 Document B

The ERG has cross checked the drug cost calculations of the CS; Table 22 Document B with the exception of infliximab.

The costing for the 1st year of treatment with adalimumab includes an initial 80mg dose followed by 26 bi-weekly 40mg doses. The last dose is at the start of the last week of the year and so covers the first week of the 2nd year. The company takes account of the unutilised dose by only applying half the cost of the final adalimumab 1st year dose. For the 1st year costing this consideration does not affect any of the other biologics.

CS; Table 22 Document B can be amended to present costs for the induction period, augmented with the drug costs for guselkumab for ease of reference. Note that the induction costs for adalimumab and etanercept include the cost of the dose that is received during the end of induction week when response is assessed. It can be argued that these should be adjusted by the treatments' PASI75 response rates.

Table 4: 1st year and induction costs and annual maintenance costs among responders

	1st year	(Induction)	Annual thereafter
Etanercept	£9,295	(£2,145)	£9,295
Etanercept biosimilar	£8,528	(£1,968)	£8,528
Adalimumab	£9,684	(£3,521)	£9,156
Ustekinumab	£10,735	(£4,294)	£9,304
Secukinumab	£18,282	(£7,313)	£14,625
Ixekizumab	£19,125	(£7,875)	£14,625
Guselkumab	[redacted]		

CS; Table 22 of Document B does not take into account the secukinumab and ixekizumab PASs. The ERG presents this in the confidential (cPAS) appendix.

Drug cost calculations: Cost comparison assuming clinical similarity

The company cost comparison may be biased against guselkumab for the comparison with adalimumab and to a lesser extent for the comparison with ustekinumab due to not taking into account the unutilised dose at the end of the time horizon. The company model with a 5-year time horizon includes all doses up to and including week 260.

- Week 260 is a dosing week for guselkumab. It can be argued that only one eighth of this cost should be applied because the following seven weeks of the eight week dosing schedule fall outside the time horizon.
- Week 256 is a dosing week for ustekinumab. It can be argued that only five twelfths of this cost should be applied because seven weeks of the twelve week dosing schedule fall outside the time horizon.
- Week 259 is a dosing week for adalimumab. The cost of this should be included as the two week dosing schedule lies within the time horizon.

The ERG will adjust the company calculations to remove the cost of the dosing that falls outside the time horizon.

This results in the following cost estimates using the company method over 5 years, and using the ERG adjustments for drug costs falling within the time horizon for time horizons of 1-year, 5 years and 10 years.

Table 5: Cost comparison with subcutaneous biologics: [redacted] costs

	Company	ERG		
	5 years	1 year	5 years	10 years
Etanercept	..	£7,643	£25,057	£33,164
Adalimumab	£25,785	£8,299	£25,785	£33,926
Ustekinumab	£27,928	£9,406	£27,553	£36,007
Secukinumab	..	£15,978	£43,414	£56,237
Ixekizumab	..	£16,581	£44,156	£56,994
Guselkumab	[redacted]			

Table 6: Cost comparison with subcutaneous biologics: [redacted] costs

	Company	ERG		
Guselkumab vs	5 years	1 year	5 years	10 years
Etanercept Adalimumab Ustekinumab Secukinumab Ixekizumab	[redacted]			

The ERG adjustments somewhat lessen the additional cost of guselkumab compared to adalimumab over the 5-year time horizon. The ERG comparison with ustekinumab is largely in line with the company estimates.

The above does not take into account the secukinumab and ixekizumab PASs. The ERG presents this in the confidential (cPAS) Appendix.

Drug cost calculations: Cost comparison differentiating clinical similarity

It is not obviously reasonable to assume clinical similarity. The ERG will explore (a) assuming similarity as per the company cost comparison and (b) applying the central estimates of the company NMA. In the light of the company cost comparison analysis being biased against guselkumab the ERG adjusts these estimates for the dosing falling outside the time horizon as previously outlined.

The STAs have often assumed a 10-year time horizon at the end of which under the company similarity scenario around 10% remain on treatment, and this will be adopted in what follows.

Sensitivity analyses are also presented:

- SA01: a 5-year time horizon at the end of which under the company similarity scenario around 30% remain on treatment; and,
- SA02: The impact of differential discontinuation rates as derived from Warren et al (2015)[13] and Iskander et al (2017).[14]

Since the above implies that the treatments are not clinically similar the cost comparison requires that [redacted]. In line with the ixekizumab submission (TA442) the ERG assumes [redacted] for those on subcutaneous biologic therapy [redacted][10]

Table 7: Cost comparison with subcutaneous biologics: total costs

	Similarity			NMA estimates		
	Base	SA01	SA02	Base	SA01	SA02
Etanercept	£38,155	£28,827	£27,797	£17,338	£13,451	£13,021
Adalimumab	£39,014	£29,631	£41,985	£32,119	£24,581	£34,506
Ustekinumab	£41,095	£31,399	£62,213	£33,432	£25,779	£50,101
Secukinumab	£61,228	£47,185	£45,791	£57,726	£44,601	£43,298
Ixekizumab	£61,985	£47,926	£94,169	£63,088	£48,741	£95,931
Guselkumab	[redacted]					

Table 8: Cost comparison with subcutaneous biologics: net costs

	Similarity			NMA estimates		
Guselkumab vs	Base	SA01	SA02	Base	SA01	SA02
Etanercept	[redacted]					
Adalimumab						
Ustekinumab						
Secukinumab						
Ixekizumab						

Given the 1st year and subsequent year [redacted] costs assuming complete clinical similarity results in net costs much as would be expected. Similarly, given the superior PASI75 for guselkumab compared to all but ixekizumab, the NMA results mean that more guselkumab patients go on to receive ongoing maintenance therapy and so the net costs increase. Only for the comparison with ixekizumab which has a similar PASI75 estimate to guselkumab are the [redacted] costs little affected by this.

[redacted]

Restricting the analysis to a 5-year time horizon predictably lessens the differences. Despite many of the STAs assuming a 10-year time horizon and later STAs assuming a lifetime horizon, as cost comparison does not involve discounting a 5-year time horizon could be argued for.

Applying the BADBIR derived discontinuation rates somewhat increases the costs of ustekinumab due to the 9% annual discontinuation rate, and also the costs of guselkumab and ixekizumab which are assumed to have the same 9% annual discontinuation rate. The costs of adalimumab are little changed given its annual 18% discontinuation rate, but the costs of etanercept fall due to its 29% discontinuation rate. The costs of secukinumab also fall somewhat due to it being assumed to have the same discontinuation rate as etanercept, based upon Egeberg et al (2017),[16] but as reviewed above this assumption may not be reliable due to the secukinumab patients in Egeberg et al being heavily pre-treated with biologics. Ignoring secukinumab, the BADBIR discontinuation rates tend to increase the net costs and the net savings.

The above does not take into account the secukinumab and ixekizumab PASs. The ERG presents this in the confidential (cPAS) appendix.

4.2 Conclusions

The company cost comparison assumes clinical similarity in terms of both PASI75 and discontinuation rates. Most of the company NMA PASI75, PASI90 and PASI100[11] relative risk estimates are statistically significant and estimate guselkumab to be the more effective treatment including those relative to adalimumab and ustekinumab, the company's chosen comparators.

The company presents the [redacted] costs for the 1st year of treatment and subsequent years which is broadly sufficient for an assessment if clinical similarity is to be assumed. As a consequence, it may not be reasonable or particularly informative for the company to assume clinical similarity for the formal cost comparison modelling for the comparisons with

[11] The central estimates for DLQI 0/1 favour secukinumab and ixekizumab, with the latter being borderline statistically significant. But cost effectiveness modelling to date has been based upon PASI responses.

adalimumab and ustekinumab, or for any comparisons with the other subcutaneous biologics with the possible exception of ixekizumab.

AbbVie's-adalimumab has a [redacted], but potentially less expensive generics likely to enter the market may ensure continued wide use of an adalimumab. Adalimumab may be of debatable future relevance for plaque psoriasis in isolation, but ERG expert opinion indicates it may continue to be of relevance due to both its well-known safety profile and its efficacy in psoriatic arthritis.

[redacted] In the light of this, the NMA considering all biologics and ixekizumab being the last biologic to be approved by NICE, the ERG presents results for the subcutaneous biologics approved by NICE.

[redacted]

The FTA guidance notes also do not specify that the comparator cannot be a treatment that is marketed by the company. Janssen markets ustekinumab. The ERG is unclear whether there are any concerns if the company can only demonstrate lower drug costs against a comparator it also markets and prices. The [redacted] costs can be assessed assuming clinical similarity. The health benefits and [redacted] costs can also be assessed at the NMA central estimates. The following is based upon PAS inclusive costs for guselkumab. But they do not include the PASs for secukinumab and ixekizumab and so are not relevant to the AC for these cost comparisons. The cost comparisons relevant to decision making are the PAS inclusive costs for guselkumab, secukinumab and ixekizumab, which are presented in the cPAS appendix.

The ERG summary of the [redacted] costs does not consider similarity in costs as there is little to judge what the AC will view as being similar and the reader is referred to the cPAS appendix.

The similarity of the patient distribution across PASI health states for guselkumab and ixekizumab at central NMA estimates means that similar proportions of patients would receive ongoing maintenance therapy and that any QALY estimates would be reasonably similar for the two treatments. As a consequence, were guselkumab to be considered within an STA it might be sufficient for the AC to focus upon the differences in the [redacted] costs as presented in the cPAS appendix with an assumption of clinical similarity.

5 ERG commentary on the robustness of evidence submitted by the company

The strengths of the submission lie in the good quality RCTs comparing guselkumab with a widely used anti-TNF agent (adalimumab) and in the exhaustive NMAs undertaken which allow comparison of guselkumab with both a full and a more focussed range of competing biologicals.

Recommendations

Overall the ERG believes that with the appropriate PASs that guselkumab compares favourably in cost comparisons with the company chosen comparators. However, the ERG considers that there are a number of uncertainties in the submission:

a) First, in the context of rapidly changing market share and clear differences in clinical effectiveness of biologicals, the ERG is uncertain that the company's choice of comparator(s) is appropriate. Both secukinumab and ixekizumab may be relevant to the decision problem and both also have PASs that are not considered in this document but are presented in the cPAS appendix;
b) Second, there are striking differences in real world withdrawal rates of different biologicals relative to the blanket 20% applied in the cost comparison exercise; the company did not explore the effect of applying separate rates to the different drugs, resulting in residual uncertainty in the cost-comparisons;
c) Third, 43 centres were common to both VOYAGE 1 (101 centres overall) and, VOYAGE 2 (115 centres overall) (see CS; Supplementary Clarification Document). This questions the independence of these studies, as assumed when performing an NMA. This is a problem that may not be unique to guselkumab and the VOYAGE

trials, but may also affect other treatments and their relevant trials included in the NMA. In mitigation, NMAs could have been conducted with just one VOYAGE trial included (with sensitivity analyses using the alternative VOYAGE trial). The ERG would anticipate that this procedure would widen the credible intervals obtained for the comparisons of guselkumab versus other therapies, but not affect the findings.

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Appendix 1: Errata in company submission

The ERG have identified the following errors within the CS.

1. CS; Table 15 document B - the bottom row is titled discontinuations due to AEs, however the numbers are instead for SAEs. The table should read as follows:

	Week 0–16			Week 16–48	Week 0–48	
	PBO	**GUS**	**ADA**	**PBO-GUS**	**GUS**	**ADA**
Patients treated, n	174	329	333	165	329	333
Discontinuations due to an AE, n (%)	2 (1.1)	4 (1.2)	3 (0.9)	1 (0.6)	9 (2.7)	12 (3.6)

2. Erelzi (etanercept biosimilar) appears in CS; Figure 28 and 29 of clarification document response (WDAE NMA) but it should not be included here. Erelzi also features in CS; Figure 9 of company's clarification document response.

3. CS; Table 15 of the clarification Response is titled: League table summary of relative risks for the PASI 90 response at the end of induction analyses; unadjusted; restricted evidence network. ERG believes this should be titled: League table summary of relative risks for the PASI **75** response at the end of induction analyses; unadjusted; restricted evidence network.

4. Additional errors identified in Tables:

Location	**Erratum**	**Correction**
Table 8 of CS Appendix	REVEAL: AE Placebo Arm: 7/398 (1.8%)	AE Placebo Arm: 211/398 (53%)
Table 8 of CS Appendix	Cai 2017: AE Adalimumab: 158/338 (28.4%)	AE Adalimumab: 158/338 (46.7%)
Table 8 of CS Appendix	PHOENIX 2: AE Ustek 90mg: 204/410 (49.8%)	AE Ustek 90mg: 197/411 (47.9%)

Table 7+8 of CS Appendix	CLEAR Trial reported as having Placebo arm	Placebo should be replaced with Ustekinumab.
Table 8 of CS Appendix	REVEAL Trial reported as Adalimumab achieving 14% PASI100	Proportion should be 20%, matching 163/814
Table 8 of CS Appendix	PHOENIX 1 Trial reported as Ustekinumab 90mg PASI75 as 36.7%	Proportion should be 66.4%, matching 170/256

Appendix 2: Discontinuation studies

Summary

The ERG has not undertaken a systematic review of discontinuation rates but has identified a number of papers that are relevant.

In the opinion of the ERG, the estimates of Warren at al (2015)[13] and Iskander et al (2017)[14] are the most relevant to the UK. These examine ustekinumab, adalimumab and etanercept and suggest annual discontinuation rates of around 9%, 18% and 29% respectively. But a systematic review by No et al[15] suggests smaller differences in annual discontinuation rates with these falling between 11-15% for these treatments.

These papers do not cover secukinumab, ixekizumab or guselkumab.

Egeberg et al (2017)[16] analyses Danish registry data that covers ustekinumab, adalimumab, etanercept and secukinumab and find secukinumab to have the highest discontinuation rate. But they caution that the secukinumab patient numbers are low and these patients were much more heavily pre-treated with 18% having had 3 prior biologics and 20% having had 4 or more prior biologics, compared to less than 5% having had 3 or more prior biologics for ustekinumab, adalimumab and etanercept.

The ERG has not identified any long term discontinuation studies for either ixekizumab or guselkumab.

Individual papers

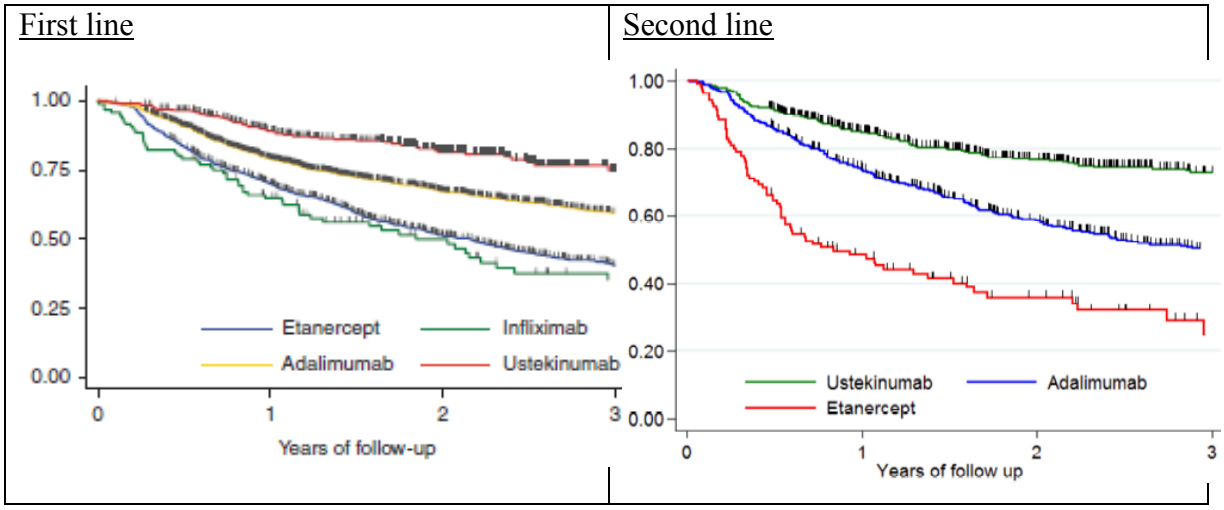
Warren et al (2015)[13] analysed the prospective cohort study data from the British Association of Dermatologists Biologic Interventions Register (BADBIR). This focussed upon the 3,523 biologic naïve patients receiving a first course of a biologic with data for infliximab (n=96), adalimumab (n=1,879), etanercept (n=1,098) and ustekinumab (n=450) being available. Their conclusion is that ustekinumab has the lowest discontinuation rate.

Based upon Figure 2 and disregarding the initial 4-month period to account for induction suggests that over the subsequent 2 years 8 months the proportion remaining on treatment is around 73% for ustekinumab, 59% for adalimumab, 54% for infliximab and 40% for

etanercept. These in turn suggest annual discontinuation rates of 11% for ustekinumab, 18% for adalimumab, 21% for infliximab and 29% for etanercept.

Iskander et al (2017),[14] with much the same authorship list as Warren et al (2015),[13] analysed the BADBIR data focussing upon 1,239 patients receiving a 2nd line biologic. They also found that at 2nd line ustekinumab has a lower discontinuation rate than adalimumab, which in turn has a lower discontinuation rate than etanercept. Based upon table 2 (and ignoring the 1st year data since it includes induction) this suggests annual discontinuation rates of 7% for ustekinumab, 18% for adalimumab and 29% for etanercept. These estimates are in line with those of Warren et al (2015)[13] for 1st line treatments, though the estimate for 2nd line ustekinumab is a slightly lower discontinuation rate than for 1st line ustekinumab. The results reported by Warren and Iskander are shown in Table 01.

Table 01: Discontinuation reported by Warren and Iskander



No et al (2017)[15] provide a systematic review of discontinuation studies and a pooled survival analysis for the first 5 years of treatment for ustekinumab, adalimumab, infliximab and etanercept. In contrast to the BADBIR data, while this suggests a lower 1st year discontinuation of 13% for ustekinumab compared to 26% for adalimumab by the 5th year the total discontinuations have equalised at 53%. Ignoring the 1st year data due to it including induction this suggests annual discontinuation rates of 14% for ustekinumab, 11% for adalimumab, 13% for infliximab and 15% for etanercept. The systematic review suggests much more similar discontinuation rates than the BADBIR data.

Egeberg et al (2017)[16] analysed data from 2,161 Danish patients with 3,495 treatment series from the DERMBIO registry. Patients received etanercept, infliximab, adalimumab, ustekinumab and secukinumab. While the Kaplan Meier curves for ustekinumab typically lie above those of adalimumab, after the 1st year they appear broadly parallel which might suggest a similar long term discontinuation rate. Egeberg et al conclude that despite secukinumab having the highest PASI100 it also had the highest discontinuation rate, while ustekinumab had the lowest discontinuation rate.

Egeberg et al (2017)[16] cautioned that the number of secukinumab treatment series was quite low at 196 secukinumab patients tended to have had more prior treatments and that this might be a reason for its high discontinuation rate. Secukinumab patients were roughly equally split into fifths who had had no prior (22%), 1 prior (22%), 2 prior (19%), 3 prior (18%) and 4 or more prior (20%) biologics. Roughly half of ustekinumab, etanercept and infliximab patients had had no prior biologic, this rising to three quarters for adalimumab. The treatments other than secukinumab also only had small percentages of patients, less than 5%, who had had 3 or more prior biologics.

Figures 1C to 1F of the main Egeberg et al paper stratify by biologic naïve and biologic experienced and suggest to the ERG that the most reasonable assumption may be to assume secukinumab has a similar discontinuation rate to etanercept. But this still fails to take into account the large differences in the numbers of previous biologics among biologic experienced secukinumab patients compared to the other treatments.

The supplementary material available on line for Egeberg et al includes Kaplan Meier plots restricted to patients with in-label dosing. This suggests that etanercept and infliximab have the worst discontinuation rates, then secukinumab, then adalimumab with ustekinumab only being slightly better than adalimumab.