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Evidence Review Group's Report
Tildrakizumab for treating moderate to severe plaque psoriasis

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Rider on responsibility for report

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Ruth Walker, Nerys Woolacott and Mark Corbett wrote the clinical effectiveness sections of the report. Nerys Woolacott took overall responsibility for the clinical effectiveness sections. Josh Carlson and Francesco Fusco wrote the cost effectiveness sections and conducted the ERG economic analyses. Kath Wright wrote the sections on the search strategies. Stephen Palmer provided advice, commented on drafts of the report and took overall responsibility for the cost effectiveness sections.

Note on the text

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List of abbreviations

AE	Adverse event
BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic Interventions Register
BID	Twice daily
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CI	Confidence interval
CPID	Clinical Practice Research Datalink
CS	Company's submission
CSR	Clinical study report
DERMBIO	Danish Biologic Interventions Registry
DIC	Deviance Information Criterion
DLQI	Dermatology Life Quality Index
DMARDs	Disease-modifying anti-rheumatic drugs
DMF	Dimethyl fumarate
DSU	Decision Support Unit
EAS	Efficacy analysis set
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol-5D questionnaire
ERG	Evidence Review Group
FAS	Full analysis set
FE	Fixed-effect
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICER	Institute for clinical and economic evaluation
mg	milligram
NAPSI	Nail Psoriasis Severity Index
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit

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NR	Not reported
NRI	Non-responder imputation
NT	Not tested
PAS	Patient access scheme
PASI	Psoriasis Area and Severity Index
PASI 50	50% or greater improvement in PASI score
PASI 75	75% or greater improvement in PASI score
PASI 90	90% or greater improvement in PASI score
PASI 100	100% improvement in PASI score (total skin clearance)
pD	Posterior mean of the deviance minus the deviance of the posterior means
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PsA	Psoriatic arthritis
PSI	Psoriasis Symptom Inventory
PUVA	Psoralen and long-wave ultraviolet radiation
QALY	Quality-adjusted life year
QoL	Quality of life
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
RCT	Randomised controlled trial
RE	Random-effects
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
sPGA	static Physician's Global Assessment
STA	Single Technology Appraisal
TA	Technology Appraisal
TEAE	Treatment emergent adverse event
TDS	Technical Support Document
TNF	Tumour necrosis factor

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1 Summary

Tildrakizumab (Ilumetri®) is a biologic therapy for treating adults with moderate-to-severe plaque psoriasis. It is a high-affinity anti IL-23p19 monoclonal antibody that selectively blocks the p19 subunit of interleukin-23. The recommended dose in adults is 100mg at Weeks 0, 4 and every 12 weeks thereafter, administered by subcutaneous injection. In patients with certain characteristics (e.g. high disease burden, body weight ≥90kg) a 200mg dose may provide greater efficacy.

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

The population specified in the NICE scope - adults with moderate to severe plaque psoriasis - is broader than the anticipated licensed indication for tildrakizumab, which is, "*adults with moderate to severe plaque psoriasis who are candidates for systemic therapy*". Furthermore, the CS decision problem considered that, tildrakizumab would be used alongside existing biologic treatment options, which in, in UK clinical practice is after non-biological systemic therapy in the treatment pathway. The ERG considers this narrower population to be appropriate and their clinical adviser confirmed that, although biological therapies such as tildrakizumab are often licensed for use earlier in the pathway, in UK clinical practice they would be used after non-biological systemic therapy.

No definition of moderate to severe psoriasis is specified in the NICE scope, but the threshold given in the NICE pathway to be considered for biological therapies is a PASI score ≥ 10 and DLQI > 10. After examining the trial inclusion criteria and baseline data for the clinical trials the ERG considers the population in the clinical evidence presented to sufficiently reflect the eligible population in England and Wales in this respect.

For comparators, the NICE scope appeared to describe two different pathway points by specifying 1) conventional systemic non-biological treatments (such as methotrexate or phototherapy) and 2) biological therapies, apremilast and dimethyl fumarate (DMF). As stated above, the ERG and the ERG's clinical adviser concur with the CS that conventional systemic therapies are not relevant comparators: only treatments recommended at the same point in the treatment pathway as biologics are relevant. The ERG considers that this means the comparators should be all other biologics, apremilast and dimethyl fumarate (DMF). However, in the CS apremilast and DMF were not included as comparators because they were deemed to be 'generally used prior to or in patients unsuitable for biologic treatments'. The CS also excluded infliximab because 'it is recommended by NICE for very severe psoriasis and positioned in a separate arm of the psoriasis treatment pathway'. Despite this the ERG notes that apremilast and DMF were included in the network meta-analyses and, following an ERG clarification question, the company did submit analyses which included infliximab.

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The decision problem addressed in the CS adhered to the following outcome measures specified in the NICE scope: severity of psoriasis; mortality; response rate; duration of response; adverse effects of treatment and health-related quality-of-life (HRQoL). However, the CS stated that for two outcomes listed in the NICE scope relevant data were not available. These were relapse rates, which were captured during off-treatment periods within the pivotal clinical studies, and were therefore not deemed relevant and 'psoriasis symptoms on the face, scalp and nails' for which data were 'not available'.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical efficacy and safety data on tildrakizumab came from three randomised trials: two phase III trials (reSURFACE1 and reSURFACE2) and one phase IIb dose-finding trial. All three trials had a placebo-controlled phase: 12 weeks for the two reSURFACE trials and 16 weeks for the Phase IIb trial. reSURFACE2 also included a randomised comparison with etanercept up to 28 weeks.

In both reSURFACE trials, at 12 weeks patients taking tildrakizumab 100mg and 200mg had statistically significantly better results than those taking placebo for the following outcomes: PASI 75 response, Physician's Global Assessment (PGA) of 'clear' or 'minimal' (the co-primary endpoints), and PASI 90 and PASI 100 response (secondary endpoints). Compared with etanercept, the tildrakizumab 100mg and 200mg groups performed statistically significantly better for all outcomes at 12 weeks and 28 weeks except for clear or minimal PGA at 12 weeks for 100mg. In both phase III RCTs, when compared with placebo, tildrakizumab was associated with statistically significant improvements in health-related quality of life, as assessed by the Dermatology Quality of life index (DLQI).

No clinically relevant differences in efficacy were observed across the pre-specified subgroup analyses - previous use of a biologic, and baseline weight ≤90kg and >90kg - for PASI 75 and PGA 'clear' or 'minimal' responses at week 12 in both reSURFACE 1 and reSURFACE 2. Results of subgroup analyses of baseline PASI score suggested a slightly better response rate in patients with baseline PASI score < 20 compared with patients with a higher PASI score (most obvious for PGA 0/1). There was no apparent effect of previous use of phototherapy and systemic non-biological therapy. The CS also examined differences between tildrakizumab doses (100mg and 200mg) within subgroups, even though the trials were not designed or powered to detect such differences. Based on week 28 data, the CS stated there was a trend towards better PASI and PGA outcomes with the 200mg tildrakizumab dose compared with the 100mg tildrakizumab dose in heavier patients (>90kg), and in patients with a baseline PASI≥20.

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The NMA presented in the CS compared the efficacy of tildrakizumab (100 mg and 200 mg) with the therapies adalimumab, apremilast, brodalumab etanercept, ixekizumab, risankizumab, guselkumab secukinumab, ustekinumab and DMF. The company also submitted a NMA including infliximab. Two analyses were conducted: one using a 12-16 week time point (Stage I) (using placebo controlled phases of trials); and one using a 24-28 week time point (Stage III) (as 24-28 week data are not placebo controlled; the Stage III network used placebo data from 12-16 weeks). A Stage II analysis of direct comparisons between active treatments only could not be run as there was no connected network. The results of the stage I NMA showed

[redacted]

The results of the Stage III NMA reveal a similar pattern of relative efficacy across tildrakizumab and its comparators as the Stage I analysis did

[redacted]

Data were presented in the CS showing that, in patients who achieved a PASI 75 response at Week 28, tildrakizumab maintains clinical efficacy at around the one-year time point; pooled data from long-term extension studies suggested that efficacy is maintained for up to three years.

The CS stated that tildrakizumab has a favourable safety profile when compared with etanercept and placebo. Discontinuation due to adverse events was low in patients treated with tildrakizumab (≤2% across all parts of reSURFACE 1 and reSURFACE 2). The most frequent adverse event up to week 12 across the trials groups receiving tildrakizumab was nasopharyngitis which ranged in incidence from around 6% to 13%. These rates were a little higher than was seen in the trial groups which received placebo (5% to 8%), though similar to the rate seen in the etanercept group (12%).

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

All three of the randomised trials of tildrakizumab appeared to be generally well-conducted. However, the reSURFACE trials' results suggest that the efficacy of tildrakizumab may not be fully realised in some patients by the 12 week primary time point used for both the trials. In the phase IIb trial the greatest efficacy for PASI 75 response was seen at 16 weeks. The EMA SmPC states that consideration should be given to stopping tildrakizumab if no response is seen after 28 weeks, so in clinical practice tildrakizumab would be taken for much longer than the 12 week primary trial time point before a decision is made on treatment success.

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Although internally valid, the two reSURFACE trials did have some limitations in terms of their generalisibility (external validity) to the population likely to receive tildrakizumab in the NHS. The proportion of patients in the two trials who had previously been treated with a biologic was only around 20% across the trials, whereas in the NHS it is unlikely that tildrakizumab would be used as a first line biologic therapy. Moreover, the proportion of patients previously treated with a systemic non-biologic therapy in both reSURFACE1 and reSURFACE2 (total across treatment arms, [redacted] and [redacted] respectively) is likely to be less than would be seen in clinical practice, where the vast majority of patients are expected to have tried systemic non-biologic therapy prior to commencing a biologic.

These concerns were explored to some extent by the subgroup analyses. At 28 weeks, but not at 12 weeks, there appeared to be a lower level of response in patients who had had a previous biologic compared with those who had not, although without confidence intervals it is difficult to draw firm conclusions. Based on the 28 week data, the ERG did not find convincing evidence of a better response with the 200 mg dose (than with 100mg) in patients weighing >90kg, as reported in the CS. For patients with a baseline PASI >20 there was a suggestion of better response with the 200mg dose at week 28.

The results presented in the CS for the longer-term phases of the reSURFACE trials are of limited value in terms of providing robust clinical effectiveness data. This is due to a lack of control groups; a lack of blinding in the long-term phases (i.e. from week 52 or week 64) and, most importantly, the use of 'as observed' datasets, which exclude many of the non-responders and dropouts. Furthermore, it is possible that for some patients the decisions made regarding the continuation or discontinuation of tildrakizumab in the longer-term phases were not reflective of those likely to be made in the NHS (as no stopping rules were reported from the time point of entry into the long-term study); this would mean the results would have limited applicability to NHS practice.

Tildrakizumab appears to have an acceptable safety profile with the incidence of treatment emergent adverse events (TEAEs), serious TEAEs, discontinuations due to AEs, and severe infections being comparable across all four trial interventions used in the two reSURFACE trials. The CS results which compared rates of adverse events in the longer-term are not likely to be reliable as they may have been subject to various biases.

Network meta-analysis

Appropriate methods were used to identify the trials for the NMA, although these were not used to identify the infliximab trials. Comparing the trials included with those included in other comparable recent NMAs indicates that the included trials are appropriate.

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The methods used for the NMA appear appropriate, although it is possible that the efficacy of adalimumab was slightly underestimated due to the selection of 12 week rather than 16 week data for a small number of trials. The Stage III (24/28 weeks) NMA is less robust and may be less reliable than the Stage I (12/16 weeks) NMA as it includes extrapolated placebo data and some uncontrolled treatment data, so firm conclusions should not be made based on the stage III analyses.

The ERG notes that the results for the company's base case Stage I NMA (outcome assessment at 12-16 weeks, random effects, not placebo adjusted) are similar to those from the ICER NMA (that included only phase III trials) except that in the ICER results adalimumab was more efficacious than tildrakizumab with less overlap of credible intervals. The results of the additional sensitivity analyses requested by the ERG (provided by the company in their clarification response) showed little difference from the main analysis. This included the analysis including infliximab (RE, non-placebo adjusted model) which the ERG considers the most appropriate analysis. From this analysis additional results found [redacted]

The results of the Stage III NMA reveal a similar pattern of relative efficacy across tildrakizumab and its comparators as that from the Stage I analysis. A simple comparison of the relative risks against placebo across the Stage I and Stage III analyses reveals that for all levels of PASI response tildrakizumab 100 mg and 200mg and all the comparators are more efficacious at week 24/28. Therefore, there does not appear to be clear evidence that improved efficacy at later time points is a benefit particular to tildrakizumab.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's search did not identify any published cost-effectiveness studies of tildrakizumab. As a result, the company developed a *de novo* cost-effectiveness model for the purposes of this appraisal. The ERG considers that the company's conclusions are appropriate and the de novo cost-effectiveness model is the only relevant source of evidence concerning the cost-effectiveness of tildrakizumab for moderate to severe plaque psoriasis.

The economic evaluation of tildrakizumab was undertaken using a Markov state-transition model developed in Microsoft Excel ®. The use of a Markov approach was justified based on the need to model treatment sequences over an appropriate time horizon.

A total of 8 treatment sequences were evaluated. These sequences include three lines of biologic therapy followed by BSC. Tildrakizumab is included in a first line position alongside other

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comparators recommended by NICE for psoriasis patients who have failed to respond to conventional systemic therapies or who are intolerant or have a contraindication to these treatments.

Tildrakizumab and each comparator treatment were then assumed to be followed by a second and a third line biologic therapy. Second- and third-line biologic therapies were selected by the company based on clinical guideline and advice. Across the majority of sequences, ustekinumab and secukinumab were included as the second and third-line treatments, respectively.

The model consists of four main treatment-related health states (induction, maintenance, best supportive care and death) with patients being allocated to one of four PASI response categories (PASI <50, PASI 50-74, PASI 75-89, PASI ≥90).

Each line of treatment in a sequence starts with an induction period lasting 14 weeks. At the end of the induction period, individuals are assigned to one of the four PASI response categories based on the NMA results. Individuals who achieve a response of PASI≥75 are assumed to continue with the same treatment and enter the maintenance phase of the model. Individuals who achieve PASI<75 are assumed to discontinue their treatment and then switch to the next treatment in the sequence starting with the induction period. The utility values during the induction period are based on the PASI response categories (PASI <50, PASI 50-74, PASI 75-89, PASI ≥90) assessed at the end of the induction period, i.e. patients immediately achieve the HRQoL associated with their PASI response.

During the maintenance period, individuals are assumed to continue to receive the same treatment and maintain the same PASI response until discontinuation, due to loss of response and/or adverse events. In line with previous NICE TAs, the company base-case assumes that individuals discontinue treatment at a constant annual rate.

Individuals who do not respond to the third line of treatment (or who initially respond but then subsequently discontinue treatment) enter the BSC state. The BSC state is not formally defined in the submission, although the resource costs estimates imply a combination of non-biologic drug therapy, phototherapy, day centre care and inpatient care. Upon entry to the BSC state, patients are distribued to PASI response categories and associated HRQoL according to the placebo response rates estimated using the NMA. Patients remain in this state until the end of the model time horizon or death. Mortality is not conditioned on treatment or PASI response and is derived from UK lifetables.

A 14-week cycle length was adopted to account for the different induction periods for the different treatments (between 12 to 16 weeks) and a half-cycle correction was applied. The 14 week cycle was chosen to represent the midpoint of the range of induction periods across the different treatments and to help simplify the model structure.

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The perspective of the analysis was the NHS and Personal Social Services (NHS & PSS). An annual discount rate of 3.5% was applied to both costs and health effects, in line with NICE guidance. A lifetime horizon (approximately 58 years) was chosen to capture all relevant differences in costs and benefits between comparators.

The measure of treatment effectiveness used in the model is the proportion of individuals achieving a specific threshold of PASI response relative to baseline. The PASI responses during the induction period were based on the company's random effect (not placebo adjusted) NMA. In the base-case analysis, it was assumed that prior biologic treatment did not modify treatment response and that the effectiveness of a drug was independent of its position in a sequence.

A constant annual discontinuation rate of 18.7% was applied in the maintenance period to all treatments (except BSC). This rate includes drop-outs for any reason (loss of response, adverse events, etc.). This rate was based on long-term drug survival rates from BADBIR, a large UK registry.

Adverse events were excluded from the model. The company justified this decision based on the low rate of adverse reactions in the tildrakizumab studies.

Outcomes of the model were expressed using quality adjusted life years (QALYs). The utility values used in the model were derived from EQ-5D-3L data collected as an exploratory endpoint in the reSURFACE 1 trial at baseline and week 12. Utility estimates were stated to have been derived using the European valuation set for EQ-5D-3L for the patient subgroup with a DLQI>10 (n=482). The utility values in the model were based on the proportion of individuals in the different PASI response categories (<50, 50-75, 75-90, ≥90) and the change in utility from baseline associated with the PASI response category.

The resource use and costs included in the model comprised drug acquisition, monitoring and BSC. The acquisition cost of tildrakizumab is based on the company's Patient Access Scheme (PAS). The costs for all the comparators were sourced from the list prices reported in the British National Formulary (BNF). The company submission does not include the confidential PAS schemes which have been approved for brodalumab, guselkumab, ixekizumab and secukinumab. The induction period cost for tildrakizumab and for all the comparators was based on a common 14 week stopping rule. The frequency of monitoring was based on NICE CG153 and were reported to be aligned with guidance from BAD. The company's base case does not include administration costs. The cost of BSC in the company's base case was based on estimates used to inform NICE CG153. Unit costs were sourced from the 2016/17 NHS Reference Costs, British National Formulary (BNF) and other published literature.

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Fully incremental cost-effectiveness ratios (ICERs) and pairwise incremental net monetary benefit (INMB) estimates for the tildrakizumab sequence compared to each comparator sequence, were reported.

In the fully incremental ICER comparison for the 100mg dose of tildrakizumab, there were 3 non-dominated (dominance and extended dominance) sequences. Of these, the least effective and lowest cost was the sequence starting with tildrakizumab (sequence 1). The ICER of the ixekizumab sequence (sequence 6) was reported to be £155,597 per QALY compared to the tildrakizumab sequence. The brodalumab sequence (sequence 7) was the most effective and most costly of the non-dominated sequences. The ICER of the brodalumab sequence versus the ixekizumab sequence was £2,817,613per QALY.

In the pairwise ICER comparisons, the company concluded that results showed that the tildrakizumab sequence (sequence 1) was the most cost-effective option at a cost-effectiveness threshold of £20,000 and £30,000 per QALY gained.

The company also presented ICER results from their probabilistic analysis. The ICERs were similar to the deterministic estimates. The company concluded that PSA results also demonstrated that the tildrakizumab sequence (sequence 1) was the most cost-effective option at a cost-effectiveness threshold of £20,000 and £30,000 per QALY gained.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG's critique identified 7 main issues:

(i) The sequences evaluated by the company were restrictive in terms of the number of sequences included and the position of tildrakizumab within these. The ERG raised concerns that modelling selective sequences could provide misleading estimates of cost-effectiveness, particularly if there are treatments included in a sequence which are not cost-effective themselves.

(ii) The NMA provided by the company did not include infliximab although it may be considered a relevant comparator and would further strengthen the network. The company provided an updated NMA including infliximab in their response to clarification questions. For this NMA, the random effect model without placebo adjustment was the best fitting model and was therefore considered to be the most appropriate for this assessment.

(iii) The company's base case evaluated tildrakizumab with a 14 week induction period as their base case. However, tildrakizumab's indication states that a 28 week induction period is appropriate. The company provided further rationale for a 28 week induction period and a

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scenario analysis evaluating the 28 week induction period. The ERG raised concerns with the way in which the 28 week induction period was implemented in the model for the subsequent treatments in the sequence. The ERG considers the 28 week induction period for tildrakizumab to be a relevant additional comparator, but a 28-week induction period is not deemed appropriate for the other treatments. Therefore, the ERG added a treatment line representing tildrakizumab with a 28 week induction period, but preserved the 14 week induction period in the other treatment lines.

(iv) The company calculated the cost of induction for tildrakizumab and for all the comparators using on a common 14 week stopping rule. The CS also stated that adjustments were made to the induction dose and the maintenance dose to ensure that the correct dose was assumed for a 14-week period. The ERG raised concerns regarding the potential bias introduced by assuming a common induction period for all treatments, rather than using the recommended induction periods. The ERG also noted some difficulties replicating the company's estimates for the maintenance period costs. The ERG considers that the model should accurately reflect the induction periods recommended for each comparator and states a strong preference for using the ERG's revised inputs.

(v) The cost of BSC in the company's base case was based on estimates used to inform NICE CG153 and supported by the company's clinical advisors. The CS also noted that two of the most recent NICE submission (TA 442 and TA511) used an alternative estimate reported by Fonia et al (2010). The relevance of these alternative sources has been extensively discussed in previous NICE TAs after which the committee concluded that BSC cost estimates were likely to be closer to Fonia et al. than to the estimates from NICE CG153.Based on considerations from previous NICE TAs, the ERG concludes that the estimates reported by Fonia et al (2010) appear more appropriate than the company's base case inputs.

(vi) The ERG identified a number of significant concerns regarding the utility data and assumptions used in the company's cost-effectiveness analysis. The ERG did not consider that the valuation approach used by the company was in accordance with the NICE reference case as it was stated to be derived from the European value set for EQ-5D-3L rather than the UK value set. The ERG also raised concerns about the company's proposed adjustment to the utility values to account for the impact of ageing including a programming error. The company's response to clarifying questions included a revised valuation approach using the UK value set and corrected the programming error. Although the ERG recognises the company's efforts to incorporate the impact of ageing with the utility calculations, the ERG does not consider that an adjustment for age is necessary in this assessment. The ERG further highlights that the baseline utility estimate is not used in the model and the minimum reference point for utility calculations is 0.72 (PASI<50). Although this might be an

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appropriate assumption to use while patients are receiving biological therapies, it may not be appropriate for the final treatment state with BSC. The ERG considers that there are significant uncertainties concerning whether these values can be generalised to patients not receiving biological therapies.

(vii) The company base case does not include any additional healthcare costs for patients who fail to respond to biologics and switch to another treatment or BSC. In the company's response to the request for clarification, the company provided an additional scenario including an additional cost of £229 which was assumed to be incurred once per treatment line during the induction cycle for all patients who achieve a PASI <75 response. The ERG considers that non-responder costs should be included. However, the ERG concludes that the appropriate estimate for the cost of non-response should be £801.50 (i.e. £229*14/4).

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

1.6.1 Strengths

The clinical effectiveness evidence was derived from three good quality placebo-controlled randomised trials, one of which also compared tildrakizumab with an active comparator (etanercept). A well conducted systematic review was used to identify trials for the NMA which compared tildrakizumab with all relevant comparators (once infliximab was added to the network).

The ERG considered the company's economic model submitted as part of the company's response to clarifying questions to meet the requirements of the NICE reference case and to be of sufficient quality. The company provided detailed and helpful responses to the ERG's points for clarification. The ERG acknowledges the additional work that the company undertook to respond to their requests.

The ERG reviewed the company's base-case, sensitivity and scenario analyses. The estimates reported in the CS document were compared to the inputs used in the model. The results of the base-case and the most relevant sensitivity analyses were successfully replicated. The logical checks performed on the model (e.g. extreme values for costs and utilities, treatment efficacy inputs equalised across treatment and comparators) confirmed the model behaved logically. The ERG identified issues in the calculation of the age-adjusted utilities, which was addressed by the company at the clarification stage.

1.6.2 Weaknesses and areas of uncertainty

The two main trials were placebo-controlled only up to 12 weeks and the comparison with etanercept was stopped at week 28. The primary time point for efficacy assessment used in the trials and the proportion of patients who had previously been treated with a biologic (around 20%) meant that the trials were limited in terms of how tildrakizumab would likely be used in the NHS.

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The 28 week NMA results are not as robust as the 12-16 week results as they were based on some uncontrolled data and the 28 week assessment time was not optimal for the comparators. There does not appear to be clear evidence that improved efficacy at later time points is a benefit which is particular to tildrakizumab.

The ERG has noted key weaknesses and areas with substantial uncertainty in the company submission. The ERG considered that the restrictive nature of the sequences compared in the model was an important limitation. The ERG proposed an alternative approach to inform the cost-effectiveness of alternative sequences using a net-benefit framework and associated net-monetary benefits (NMB) rankings of each individual treatment compared to BSC, to inform:

(i) whether a specific treatment has the potential to be cost-effective within a sequence (i.e. whether a particular treatment appears cost-effective compared to BSC); and

(ii) the optimal positioning of a treatment in a sequence (i.e. whether a particular treatment appears more or less cost-effective than another active comparator).

The ERG noted that there is remaining uncertainty regarding the appropriate induction period for Tildrakizumab (14 vs. 28 weeks). The ERG considers the 28 week induction period for tildrakizumab to be a relevant additional comparator and has included it as such in its exploratory analyses.

The ERG noted concerns about the approach to HRQoL including the original valuation set used, the company's proposed age adjustment, and assumption about the utilities during BSC. The ERG consider the UK valuation set (included in the company's response) to be appropriate. The ERG does not consider that an adjustment for age is necessary in this assessment. The ERG considers that there are significant uncertainties concerning the use of utilities derived from patients who are on biologic therapies for patients not receiving biological therapies, i.e. patients received BSC.

The ERG noted concerns about the use of BSC costs based on estimates used to inform NICE CG153 versus those estimated using Fonia et al (2010). Based on considerations from previous NICE TAs, the ERG concludes that the estimates reported by Fonia et al (2010) appear more appropriate than the company's base case inputs.

The ERG also notes uncertainty regarding the comparison with adalimumab. The ERG notes that the differences in effects were small and the direction of the effect changed when a placebo adjustment was used in the NMA. In addition, the cost differences may be substantially altered when the biosimilar for adalimumab becomes available in the very near future.

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1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The key uncertainties identified by the ERG were explored in 10 separate scenarios. The issues related to the sequencing of treatments were explored by evaluating initial treatment followed by BSC and estimating net benefit rankings at £20,000 and £30,000. Tildrakizumab with a 14 week induction period was ranked 1st at both thresholds when using the preferred NMA that included infliximab, a random effect model and no placebo adjustment. Adalimumab was ranked 1st at £30,000 using the same model with placebo adjustment. When a 28 week stopping rule for tildrakizumab was included as a comparator using the Stage III (24/28 weeks) NMA, tildrakizumab 100mg (28 week) became the top ranked option at both thresholds. Using the Fonia et al. BSC costs had a large impact making etanercept the highest ranked option. Changing the induction and maintenance costs, removing the age adjustment and including the cost of non response had no impact on the NB rankings.

An ERG base-case was included that used the NMA that included infliximab, a random effect model and no placebo adjustment. It also included both the 14 week and 28 week tildrakizumab stopping rule options as comparators, used the ERG adjusted costs for the induction and maintenance costs, excluded the age adjustments, used Fonia et al. based BSC costs, and included a cost for non responders. The treatment rankings according the NMB identified in the ERG alternative base-case had etanercept ranked 1st followed by tildrakizumab 14 week, adalimumab, and tildrakizumab 28 week.

In the fully incremental ICER comparison there were four non-dominated (dominance and extended dominance) sequences. Of these, the least effective and lowest cost was the sequence starting with etanercept. The ICER of the tildrakizumab 100mg (14 week) sequence was £39,683 per QALY compared to the etanercept sequence. The ICER of the tildrakizumab 100mg (28 week) sequence was £40,470 per QALY compared to the tildrakizumab 100mg (14 week) week sequence. Finally, the ixekizumab sequence (sequence 6) was the most effective and most costly of the non-dominated sequences. The ICER of the ixekizumab sequence versus the tildrakizumab 100mg (28 week) sequence was £412,418 per QALY. The difference between the results of the company base case and the ERG base case were mainly due to different estimates of the cost of BSC.

These ICERs improved in the fully incremental ICER comparison that included the additional assumption that the utility of BSC = baseline utility. Etanercept remained the least effective and lowest cost sequence. The ICER for tildrakizumab 100mg (14 week) sequence was £21,612 per QALY compared to the etanercept sequence. The ICER for the tildrakizumab 100mg (28 week) sequence was £22,342 per QALY compared to the tildrakizumab 100mg (14 week) week sequence. Finally, the ICER for the ixekizumab sequence versus the tildrakizumab 100mg (28 week) sequence was £254,261 per QALY.

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The ERG concludes that both tildrakizumab 100mg 14 weeks and 28 weeks exceed NICE's conventional cost-effective thresholds. If there is strong support for the assumption that patients receiving BSC return to their baseline utility, both tildrakizumab options fall below the £30,000 threshold.

However, these results exclude the confidential patient access schemes (PAS) for several comparators (brodalumab, guselkumab, ixekizumab and secukinumab). The impact of including these confidential PAS schemes is presented in a separate confidential appendix.

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2 Background

2.1 Critique of company's description of underlying health problem.

The company submission (CS) presented a short but adequate description of moderate to severe plaque psoriasis. The CS briefly summarises the main points:

- Psoriasis is a chronic, inflammatory, immune-mediated skin disease with an unpredictable course of flare-ups and remissions;
- Plaque psoriasis is characterised by well-delineated red, scaly plaques that typically affect the knees, elbows, trunk and scalp but may extend to other areas and these lesions, which can be itchy and painful, can cause physical and emotional discomfort;
- Plaque psoriasis significantly affects physical, emotional and psychological well-being, may lead to substantial burden in terms of disability or psychosocial stigmatisation[1] and negatively affects quality-of-life (QoL);
- Psoriasis can be classified as mild or moderate to severe depending on location, surface area affected and severity of its clinical signs, as well as impact on the patient's QoL;
- Patients with moderate to severe disease have an increased overall mortality risk and an increased risk of psoriatic arthritis, metabolic syndrome (including cardiovascular disease) and psychological disorders (anxiety, depression), which can limit social interactions..

The CS reports a figure of 1.75% for the prevalence of adult psoriasis in England and Wales. However, the ERG notes that this is derived from a systematic review of studies published between 1996 and 2011[2] A recently published cohort study based on a UK population (Clinical Practice Research Datalink (CPDR) data) reported the 2013 prevalence to be 2.3%.[3] Therefore the estimate of the number of patients with moderate to severe plaque psoriasis presented in the CS of 150,000 people, may be an underestimate.

2.2 Critique of company's overview of current service provision

The CS presented an overview of current service provision that is appropriate and relevant to the decision problem under consideration: it focussed on systemic treatment for psoriasis. The CS presented psoriasis pathways from both NICE and the British Association of Dermatologists (BAD) (see CS Figures 1, 2 and 3). In brief, whilst topical therapy and phototherapy is used for the treatment of psoriasis, moderate to severe plaque psoriasis generally requires systemic therapy [4]. First-line systemic therapy includes non-biological agents, usually methotrexate or ciclosporin. If response to these is inadequate or fails then biological therapies are indicated: (in alphabetical order) adalimumab, brodalumab, etanercept, guselkumab, ixekizumab, secukinumab and ustekinumab. In addition infliximab is recommended if the disease is very severe, as defined by a total PASI of 20 or more and

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a Dermatology Life Quality Index (DLQI) of more than 18 (NICE TA134). NICE has also recommended two other non-biologic systemic agents at this point in the treatment pathway: apremilast and dimethyl fumarate (DMF). The BAD guideline provides more detailed guidance on the use of biologics (CS Figure 3). It recommends adalimumab or ustekinumab first line (adalimumab if the patient has psoriatic arthritis). If a response is not achieved the dose can be reviewed, or the biologic switched. This can be repeated as necessary, tailoring treatment to the needs of the patient.

The CS does not present a strong case for a need for tildrakizumab. It is a high affinity, humanised immunoglobulin antibody that specifically binds to and neutralises IL-23p19 and the infrequent 12 week dosing may be considered helpful for some patients. However, the ERG notes that tildrakizumab is not unique in these: guselkumab has the same mode of action (See CS Figure 4) and ustekinumab has the same dosing regimen.

3 Critique of company's definition of decision problem

3.1 Population

The population specified in the NICE scope is adults with moderate to severe plaque psoriasis. As the anticipated licensed indication for tildrakizumab will be, "*Adults with moderate to severe plaque psoriasis who are candidates for systemic therapy*", the decision problem addressed this more specific population. The ERG notes that under comparators, the CS DP states that, "In clinical practice, tildrakizumab is expected to be used as an additional option alongside existing biologic treatment options." The ERG suggests that this means only candidates for biologic therapy should be included in the relevant population. The clinical adviser to the ERG confirmed that, although biological therapies such as tildrakizumab are often licensed for use earlier in the pathway, in UK clinical practice they would be used after non-biological systemic therapy in the treatment pathway: NICE guidance states that unless a patient cannot tolerate them, two standard systemic therapies are tried prior to biologics. This criterion is in addition to PASI 10 and DLQI 10.

No definition of moderate to severe psoriasis is specified in the NICE scope, but the threshold given in the NICE pathway to be considered for other biological therapies, apremilast and DMF is a PASI score ≥ 10 and DLQI > 10.[4] The inclusion criteria for the clinical trials presented in the submission specified a PASI score ≥ 12 with no inclusion criteria stated in relation to DLQI score. The mean baseline DLQI scores for the different treatment groups across the Phase III trials ranged from 13.2 to 14.8. The ERG considers the population in the clinical evidence presented to sufficiently reflect the eligible population in England and Wales in this respect.

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3.2 Intervention

The intervention in the NICE scope is tildrakizumab and the CS DP does not expand upon this. The anticipated licence is for tildrakizumab administered by subcutaneous injection at a recommended dose in adults of 100mg at Weeks 0, 4 and every 12 weeks thereafter. The anticipated licence also states that, 'In patients with certain characteristics (e.g. high disease burden, body weight ≥90kg) 200mg may provide greater efficacy'. It is unclear whether the 200mg dose will be used at induction in such patients or after a lack of response to the 100mg dose. Both the 100 mg and 200mg doses are studied in the clinical trials. In the Phase III clinical trials the primary assessment point is at 12 weeks. However, the draft SmPC states that,

> "*Consideration should be given to discontinuing treatment in patients who have shown no response after 28 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 28 weeks.* "

3.3 Comparators

The NICE scope included two sets of comparators. Firstly, if systemic non-biological treatment or phototherapy is suitable, systemic non-biological therapies (including methotrexate, ciclosporin and acitretin), and phototherapy with or without psoralen, were listed as comparators. However, as stated in section 3.1 above, in the CS it is stated that, 'In clinical practice, tildrakizumab is expected to be used as an additional option alongside existing biologic treatment options'. Therefore these comparators are not relevant and are not included in the CS. As stated above, the clinical adviser to the ERG concurs with this: tildrakizumab will be used instead of another biologic; the comparators therefore need to be the other biologics. Also, it is in line with NICE guidance for other biological therapies in psoriasis. However, the clinical adviser to the ERG noted further that in the future, if the price of biologics became low enough, then they might be used earlier in the treatment pathway, despite the NICE guidance.

Secondly, comparators where conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated are: TNF-alpha inhibitors (adalimumab, etanercept and infliximab); IL-17 inhibitors (brodalumab, ixekizumab and secukinumab); IL-23 inhibitor (guselkumab); IL-12/IL-23 inhibitor (ustekinumab); Apremilast; Dimethyl fumarate (DMF); and best supportive care (BSC). In the CS, apremilast and DMF are discounted as comparators. The CS states that, 'Apremilast and DMF are not direct comparators as they are positioned in a different part of the NICE psoriasis treatment pathway and generally used prior to or in patients unsuitable for biologic treatments'. The ERG does not agree with this: although the NICE Guideline does not group these two drugs with the biological agents, in NICE TA guidance both apremilast (TA 419) and DMF (TA 475) are recommended at exactly the same point as biologicals, i.e. the disease is severe, as

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defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 and has not responded to other systemic therapies, including, ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet A radiation), or these options are contraindicated or not tolerated. The clinical adviser to the ERG agreed with this, but again pointed out that price might dictate the use of these agents prior to the biologics. The ERG notes that apremilast and DMF were included in the network meta-analysis (see Section 4.1.2).

Furthermore, the CS decision problem has excluded infliximab, stating that, 'In clinical practice infliximab is not expected to be a comparator as it is recommended by NICE for very severe psoriasis and positioned in a separate arm of the psoriasis treatment pathway.' The ERG notes that although it is correct that in its TA guidance for infliximab NICE specified that infliximab is recommended only if the disease is very severe as defined by a total Psoriasis Area Severity Index (PASI) of 20 or more and a Dermatology Life Quality Index (DLQI) of more than 18, this sub-group of patients are encompassed by the NICE scope, and the CS reports subgroup results for patients whose PASI is ≥ 20. In addition, infliximab has been included as a comparator in all previous NICE appraisals for biological therapies. The ERG requested from the company further justification for the exclusion of infliximab from the submission and in their clarification response the company stated,

"*In considering whether infliximab should be a comparator for this appraisal Almirall was initially guided by the fact that infliximab is positioned in a different part of the NICE treatment pathway compared to all other biologic agents for psoriasis. NICE has assessed infliximab as cost effective in subjects with very severe plaque psoriasis, which is define by NICE as PASI ≥20 and DLQI >18 (NICE TA 134). Other aspects relating to infliximab also influenced our decision including:*

- *Infliximab is given as an intravenous infusion in a hospital setting only, rather than as a simple subcutaneous injection that can be self-administered at home.*
- *Infliximab is also associated with a significantly greater adverse event burden and risk than tildrakizumab.*

This combination of factors means that, in clinical practice, infliximab is only a suitable treatment option for a limited group of subjects, who: meet the NICE criteria; and, importantly, are willing to tolerate an intravenous infusion and are willing to risk a treatment with a relatively high adverse event profile, and are willing and able to attend hospital on an 8 weekly basis, long term. (These are additional hospital visits that are not required for tildrakizumab treatment or monitoring).

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Further, we presented the proposed group of comparators to clinical experts at a UK Advisory Board meeting and they agreed that the list of comparators without infliximab represented the most appropriate group of comparators for this appraisal based on clinical practice.

In reviewing all the above points we concluded that, based on its position in the NICE psoriasis treatment pathway, the sub-population of suitable subjects and how it is used in clinical practice, infliximab is not an appropriate comparator treatment for this assessment of tildrakizumab."

Whilst the ERG accepts these points made by the company, they do not negate the earlier points made by the ERG. The ERG concludes that apremilast, DMF and infliximab should be included in the company's decision problem. As part of their clarification response the company did provide analyses (Network meta-analysis (NMA) and economic modelling) including infliximab.

3.4 Outcomes

The outcome measures specified in the NICE scope were: severity of psoriasis; psoriasis symptoms on the face, scalp, nails and joints; mortality; response rate; duration of response; relapse rate; adverse effects of treatment; health-related quality-of-life (HRQoL). Severity of psoriasis and response rate were presented as in terms of PASI and PGA minimal or clear. Duration of response was presented as maintenance of response rate. Relapse rates were captured during off-treatment periods within the pivotal clinical studies and are therefore not included in the submission. Data on the outcome 'psoriasis symptoms on the face, scalp and nails' are not available for tildrakizumab.

3.5 Other relevant factors

The CS includes a Patient Access Scheme (PAS): a simple discount of [redacted]

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4 Clinical Effectiveness

This section contains a critique of the methods of the review of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies.

4.1 Critique of the methods of review

A systematic review to identify relevant trials of effectiveness was conducted and reported in Section B2.1 and Appendix D of the CS. The systematic review encompassed both tildrakizumab and all the treatments to be included in the NMA (see Section 4.3 for further details and discussion of the NMA).

4.1.1 Searches

The databases used for the effectiveness review of tildrakizumab and for the NMA (MEDLINE, MEDLINE in Process and MEDLINE Daily ePub Ahead of Print; Embase; Cochrane Central Register of Controlled Trials (CENTRAL); Cochrane Database of Systematic Reviews (CDSR); Health Technology Assessment; ClinicalTrials.gov; WHO International Clinical Trials Registry Platform (WHO ICTRP)) are suitable to ensure that all relevant records are identified

Additional searches of conference websites were carried out to identify potentially relevant posters and abstracts and the reference lists of identified studies were reviewed

The search strategies used in each of the databases are fully reproduced in CS Appendix D Figure 1 and Figure 6 with the date of the search being given as well as the numbers of records retrieved from each of databases. The methods used to search and scan conference websites are also described in detail.

The numbers of records identified from the various sources matches the numbers given in the PRISMA flow diagram (CS Appendix D Figure 2) and in the text on CS Appendix D page 47.

To identify tildrakizumab trials the search strategy used in all of the database searches consists simply of the term “tildrakizumab” and synonyms. This is entirely appropriate as all the numbers retrieved are relatively small so there is no need to make use of a search filter within the strategy. To identify trials for the NMA the search strategy used in all of the database searches consists of three sections combined using AND: 1) terms for psoriasis; 2) terms for selected drugs interventions; and 3) a validated RCT search filter. This is very comprehensive and uses a wide range of thesaurus and free text terms to identify reports of RCTs.

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4.1.2 Inclusion criteria

The inclusion and exclusion criteria, used to select studies for inclusion in the systematic review of effectiveness are detailed in CS Table 3. The ERG considers these criteria to be appropriate, with the exception of the comparators. The ERG notes that apremilast and DMF were included in the review despite being excluded from the company's decision problem; infliximab (also excluded from the company's decision problem) was not included. Despite not being included in the NICE scope or the company's decision problem a new biologic risankizumab was included. The company noted that the review was conducted for use on a global basis and so includes a broader base of comparators than was required for this submission. In their clarification response the company further explained that in the NMA, risankizumab was included in one arm in two studies that also explored ustekinumab (UltiMMa-1 and UltiMMa-2): these trials were included because they provided additional ustekinumab data, not because they included risankizumab.

The ERG notes with interest that another biologic under consideration for the treatment of psoriasis, certolizumab pegol, was not included in the systematic review. Hence, in terms of comparators, the systematic review neither adhered to the NICE scope, nor the company's decision problem, nor did it include all relevant comparators (irrespective of licensing or NICE recommendations), which can be considered methodologically desirable.

4.1.3 Critique of data extraction

The methods of data extraction are reported in the CS Section (appendix) D.4 and were appropriate.

4.1.4 Quality assessment

The quality assessment of the studies identified for inclusion in the systematic review of effectiveness is reported in the Appendix Section 5. The assessment considered the following factors relating to quality and the risk of bias:

- Was randomisation method adequate?
- Was the allocation adequately concealed?
- Were groups similar at the outset of the study in terms of prognostic factors?
- Were care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that that the authors measured more outcomes than they reported?

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- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
- Also consider whether the authors of the study publication declared any conflicts of interest

This assessment appears to have been appropriate and well conducted, with detailed information provided in Appendix D.5, Table 6. Details and further commentary on the results of this assessment relating to the tildrakizumab trials are given in Section 4.2.2, and to the comparators treatments' trials included in the NMA in CS Appendix D, Table 21.

4.1.5 Evidence synthesis

The evidence synthesis presented in the CS was a network meta-analysis (NMA). Details and further commentary on this analysis and the results are given in Section 4.4.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The submission included three RCTs of tildrakizumab: two phase III trials reSURFACE1 and reSURFACE2, and one Phase IIb trial. In the CS, only the two phase III trials were presented in detail, but all three trials were included in the evidence synthesis. Further methodological information regarding the phase IIb trial was provided, at request, in the company's response to clarification. The ERG discusses all three trials in this section.

4.2.1 Relevant phase III trials

The phase III trials reSURFACE1 and reSURFACE2 were presented as the main evidence for the efficacy and safety of tildrakizumab 100mg and 200mg. They are summarised below in Table 1, Figure 1 and Figure 2. Both were international, multicentre, randomised, double blind, placebo controlled, parallel group studies, with the same population: both studies included adults with moderate to severe plaque psoriasis defined as BSA involvement ≥10%, PGA score ≥3 and PASI ≥12.

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Table 1. Summary of efficacy trials reSURFACE1 and reSURFACE2 (adapted from CS Tables 5 and 6)

Study	reSURFACE1	reSURFACE2
Study design	International three-part, phase III randomised, double-blind, placebo-controlled, parallel-group, multicentre study.	
Study duration	64 week study (plus a 20 week follow-up period).	52 week study (plus a 20 week follow-up period).
Population	772 patients, 18 years or older, with moderate to severe chronic plaque psoriasis defined as BSA involvement ≥10%, PGA score ≥3 and PASI score ≥12.	1,090 patients 18 years or older with moderate-to-severe chronic plaque psoriasis defined as BSA involvement ≥10%, PGA score ≥3 and PASI score ≥12.
Intervention(s)	Tildrakizumab 100mg, tildrakizumab 200mg.	
Comparator(s)	Placebo.	Placebo and etanercept 50mg.
Co-primary end-points	The proportion of participants achieving at PASI 75 response at Week 12. The proportion of participants achieving a PGA score of 'clear' or 'minimal', with at least a two-grade reduction from baseline at Week 12.	
Key secondary end-points	Key secondary endpoints: Protocol-defined key secondary endpoints were PASI 90 and PASI 100 response at Week 12. Other secondary endpoints were proportion of patients with a DLQI score of 0 or 1 at Weeks 12 and 28, and the PASI 75 response in patients receiving continuous treatment with tildrakizumab from baseline to the end of Week 64.	Key secondary endpoints: Protocol-defined key secondary endpoints were PASI 90 and PASI 100 response at Week 12 and PASI 75 and PGA response at Week 28. Other secondary endpoints were proportion of patients with a DLQI score of 0 or 1 at Weeks 12 and 28 and a PASI 75 response in patients receiving continuous treatment with tildrakizumab from baseline to the end of Week 52.
Additional outcomes used in the economic modelling	PASI 50 and 90 at week 12 The proportion of patients achieving a PASI 50, 75 and 90 response at Week 28 EQ-5D data	PASI 50 and 90 at week 12 The proportion of patients achieving a PASI 50, 75 and 90 response at Week 28

These two RCT's differed in terms of comparators: reSURFACE1 compared tildrakizumab 100mg and tildrakizumab 200mg with placebo; reSURFACE2 compared tildrakizumab 100mg and tildrakizumab 200mg to placebo and included a comparison with etanercept 50mg.

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Trial design

Schematic diagrams detailing information on the trial design for reSURFACE1 and reSURFACE2 are presented in Figure 1 and Figure 2.

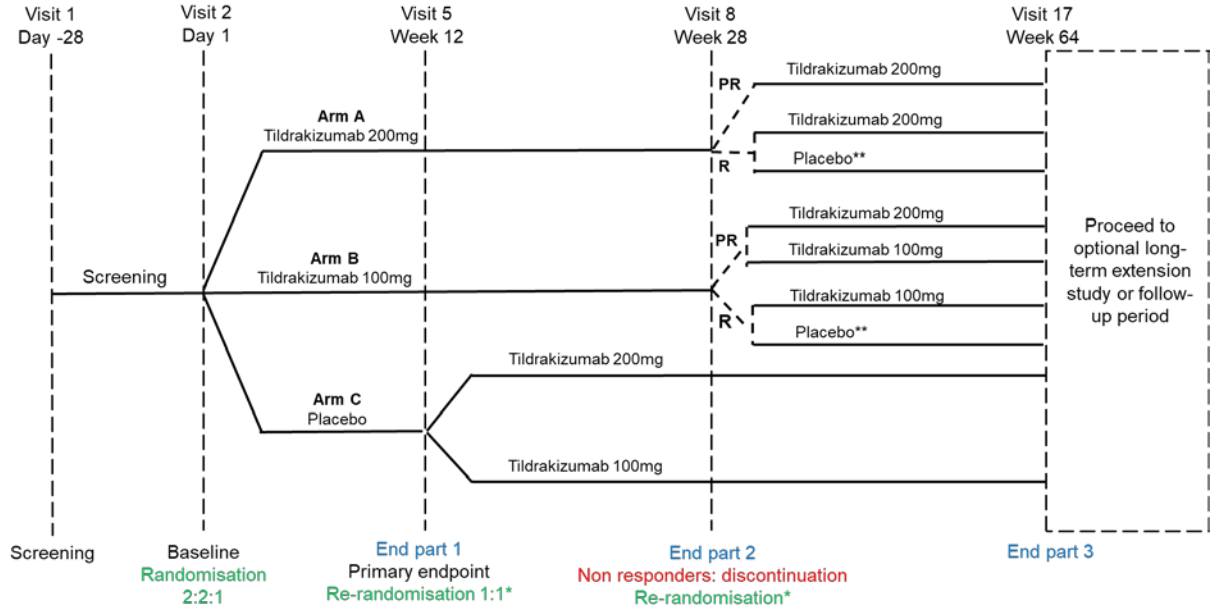

Figure 1 reSURFACE 1 study design (CS Figure 5, page 26 CS)

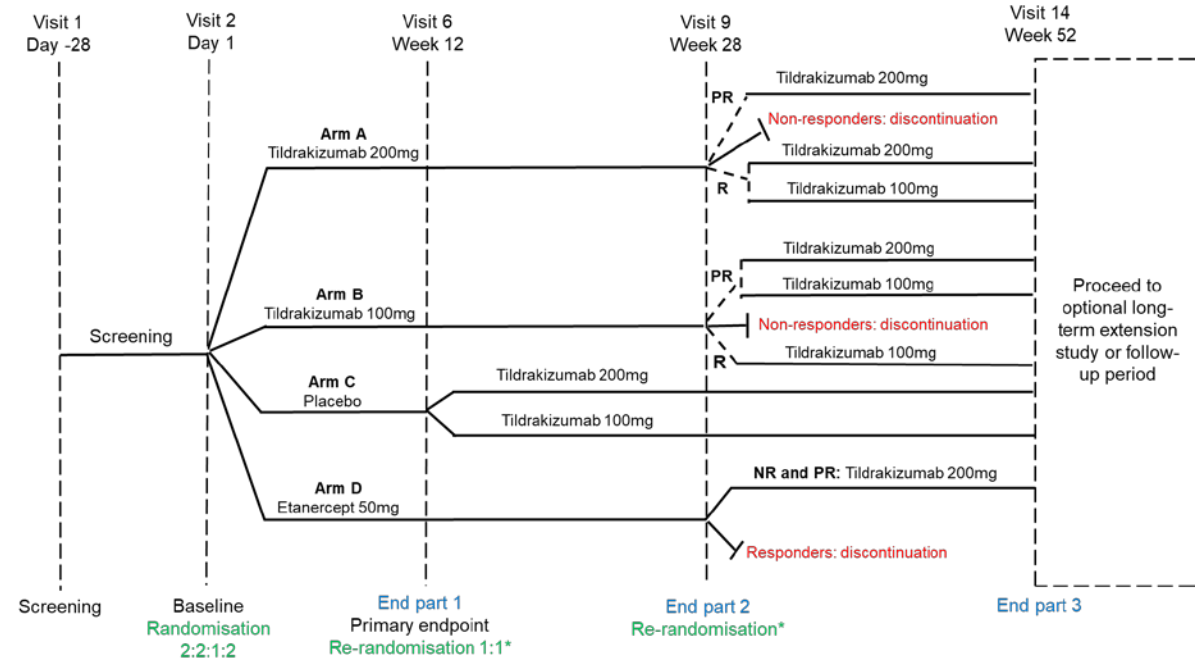

Figure 2 reSURFACE2 study design (CS Figure 6, page 27 of the CS)

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The trial designs are summarised as follows. In both trials the primary assessment point was 12 weeks. At 12 weeks patients randomised to placebo were re-randomised to either 100mg or 200mg tildrakizumab; the initial randomised active treatments continued to week 28. In both trials, at week 28 non-responders (<50% PASI improvement) to tildrakizumab were discontinued, but responders (≥75% PASI improvement) and partial responders (≥50% but <75% PASI improvement) were treated differently in the two trials:

- In re SURFACE1, responders were re-randomised to their tildrakizumab dose or placebo. Partial responders on 100mg tildrakizumab switched to 200mg. Partial responders on 200mg continued on the 200mg dose.
- In reSURFACE2 responders to 100mg continued on this dose. Responders to 200mg were re-randomised to tildrakizumab 100mg or 200mg. Partial responders on 100mg tildrakizumab were re-randomised to tildrakizumab 100mg or 200mg. Partial responders on 200mg continued on the 200mg dose. Non responders and partial responders to etanercept were switched to tildrakizumab 200mg. responders to etanercept were discontinued.

In reSURFACE1, long-term follow-up continued until week 64; in reSURFACE2 it continued to week 52.

Inclusion criteria

The inclusion criteria for both trials were: adults aged ≥18 years, diagnosis of predominantly plaque psoriasis for ≥6 months (as determined by subject interview and confirmation of diagnosis through physical examination by investigator), considered to be a candidate for phototherapy or systemic therapy, psoriasis with a BSA involvement ≥10% at baseline (Visit 2), PASI score ≥12 at baseline (Visit 2) and PGA of at least moderate disease (≥3) at baseline (Visit 2). The ERG have checked the full inclusion and exclusion criteria that are detailed in the clinical study reports, these seem reasonable and appropriate for both reSURFACE1 and reSURFACE2.

4.2.1.2 Analyses sets and statistical methods

For both trials, the analysis of efficacy was based on the full analysis set (FAS); this had been specified in the protocols of both trials. For both trials the FAS for the analysis of data up to 12 weeks inpart 1 (the placebo controlled phase of the trials) was ‘all patients who have received at least one dose of the study medication’ (reSURFACE1 - tildrakizumab 100mg n=309, tildrakizumab 200mg n=308, placebo n=154; reSURFACE2 - tildrakizumab 100mg n=307, tildrakizumab 200mg n=314, placebo n=156, etanercept n=313). For the analysis of the 12 to 28 weeks’ data (Part 2 of the trials) it was ‘patients who had completed part one, entered part 2, and received at least one dose of the study

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medication, (for placebo patients who were re-randomised, the FAS included patients who entered Part 2 and received at least one dose of study medication)' .

The statistical methods used in reSURFACE1 and reSURFACE2 are summarised in section B.2.4 in the CS. For both trials, the statistical methods were broadly were similar and appropriate. For the analysis of efficacy in the placebo-control phase of the trials, patients with missing data were imputed as non-responder data. Patients withdrawing from the either trial for any reason were considered to have discontinued the study prematurely and these individuals were not replaced. To control the overall Type 1 error rate a step-down multiplicity strategy was used (gate-keeping sequential testing procedure).

For primary end-points, both trials had more than 99% power to detect a 57% difference between tildrakizumab and placebo in PASI 75 response rate and to detect a 55% difference in proportion of subjects with PGA 'clear' or 'minimal' with at least a two-grade reduction from baseline. In addition, reSURFACE2 had 98% power to detect a difference of 17% between a tildrakizumab dose and etanercept for PASI 75 response rate and more than 99% power to detect a difference of 20% between a tildrakizumab dose and etanercept for PGA 'clear' or 'minimal' with at least a two-grade reduction from baseline.

4.2.2 Assessment of study quality

Details of the assessment of quality for reSURFACE1 and reSURFACE2 were detailed in section B.2.5 of the CS and in Appendix D, section D.5. Quality assessment of reSURFACE1 and reSURFACE2 was informed by the NICE quality assessment questions. All quality assessment criterion were assigned low for both trials, except 'declaration of any conflicts of interest', which was assigned 'high risk' for both reSURFACE1 and reSURFACE2. The ERG agrees with the quality/risk of bias assessment. The ERG notes that the high risk of bias assigned to the conflict on interest was explained in the CS stating that 'All study authors for the reSURFACE trials were paid consultants for Merck & Co, or were employees of the company.' The ERG notes that, in Reich et al. 2017 publication [5], which reports on both reSURFACE1 and reSURFACE2, this conflict of interest was declared.

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Table 2 Summary of quality assessment of reSURFACE1 and reSURFACE2. Adapted from Table 10, section B.2.5 of the CS.

reSURFACE1 & reSURFACE2 Quality assessment criterion	Risk of bias judgement in CS	ERG comment
Was the randomisation method adequate?	Low risk	Yes- Parexel International, the contract research organisation, generated computer generated randomisation sequences.
Was the allocation adequately concealed?	Low risk	Yes- an interactive voice-response system and interactive web-response system was used by Parexel to allocate participants to groups.
Were the groups similar at the outset of the study in terms of prognostic factors?	Low risk	Yes- baseline characteristics appear to be similar between treatment groups in both reSURFACE1 and reSURFACE2.
Were the care providers, participants and outcomes assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Low risk	Yes- Investigators, participants, and study personnel were blinded to group allocation and remained blinded until completion of the studies. A double-masking technique was used, in which tildrakizumab and its matching placebo or etanercept and its matching placebo were identical in appearance and packaging. Additional placebo doses were administered to maintain masking. The team doing the analysis was blinded until the database was locked.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Low risk	<10% drop out in phase one of reSURFACE1 and reSURFACE2. <15% drop out in phase two of reSURFACE1 and reSURFACE2. Reasons detailed in appendix D.5.
Is there any evidence to suggested that that the authors measured more outcomes than they reported?	Low risk	Results for key efficacy end-points reported in Reich et al. 2017 for reSURFACE1 and reSURFACE2.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low risk	Only FAS presented in CS. Missing data imputed as non-responders. FAS population identical to IIT in phase one of reUSRFACE1 and reSURFACE1.
Also consider whether the authors of the study publication declared any conflicts of interest	High risk	Conflicts of interest declared in trial publication.

4.2.2.1 Comments on design

The ERG notes that the design of reSURFACE1 and reSURFACE2 is appropriate to inform questions regarding the efficacy of tildrakizumab: the study design, inclusion criteria and outcomes assessed are broadly appropriate. The CS details some limitations of the studies, including the placebo-controlled phase being limited to 12 weeks: it is stated that the 12 week time point might have been too early to assess the efficacy potential of tildrakizumab. The ERG agree this assessment duration is limited and note that at 12 weeks patients will have received only two doses of tildrakizumab: at weeks 0 and week 4. In the anticipated licence (smPC) the recommended assessment time (stopping rule) is at week 28. The response rates at different time points are discussed in section 4.2.6. In clinical practice, tildrakizumab would be taken long-term, whilst limited, the clinical adviser to the ERG thought this

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study design to be reasonable and that enrolling patients into studies with a longer placebo-controlled phase would be challenging.

The CS also states that 'non-responders in the tildrakizumab groups discontinued treatment before Part 3, thus, there was low dropout because patients had already shown a response to tildrakizumab within 28 weeks of treatment'. The ERG agrees that the number of patients discontinuing treatment during part 3 of the trial would not reflect that in clinical practice. See section 4.2.8 for further detail.

4.2.3 Results in reSURFACE1

4.2.3.1 Participant flow in reSURFACE1

Participant flow in reSURFACE1 is presented in Appendix D, figure 4. To summarise, 772 patients were randomised, 744 (96.4%) of patients completed part one (up to 12 weeks) of the trial (tildrakizumab 200mg 298/308 (96.8%), tildrakizumab 100mg 300/309 (97.1%), placebo 146/155 (94.2%)). Thus discontinuation in Part 1 was low in all trial arms.

At 12 weeks patients were assessed for response to treatment with non-responders (those with a PASI <50) discontinued. A total of 743 patients commenced Part 2 (12 -28 weeks) of the trial, with 676 patients completing this phase (tildrakizumab 200mg 279/298 (93.6%), tildrakizumab 100mg 268/299 (89.6%), placebo re-randomised to tildrakizumab 200mg 62/72 (86.1%), placebo re-randomised to tildrakizumab 100mg 67/74 (90.5%)).

Patient baseline characteristics for reSURFACE1 are presented in section B.2.2, Table 8 of the CS. These were similar across trial arms. The trial had a higher proportion of men compared to women in the tildrakizumab 100mg, tildrakizumab 200mg and placebo arm; 67%, 73% and 65%, respectively. The majority of the participants were white; 70%, 68% and 65%, respectively. Mean± SD baseline PASI score was 20.0 (7.85), 20.7 (8.51), 19.3 (7.07), respectively. The clinical adviser to the ERG felt that the proportion of patients presenting with a baseline PASI score of >20 would be low. Data published on the demographics, disease severity and comorbidities of patients with psoriasis on enrolment into The British Association of Dermatologists Biologic Interventions Register (BADBIR) show 22.9% of patients have severe psoriasis at enrolment prior to the use of biologic therapy. Of those who had previously used biologic therapy at enrollment, 27.2% had severe psoriasis. As tildrakizumab may be given to patients who have previously used biologics, the proportion of patients presenting with a baseline PASI >20 may be higher in clinical practice in the UK than is seen in reSURFACE1.[6]

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Mean(SD) baseline DLQI scores were provided in response to clarification, these score were similar across arms, tildrakizumab 100mg, 13.9 (6.68), tildrakizumab 200mg 13.2 (6.87) and placebo 13.2 (7.25). Additionally, 23% of patients in each of the trial arms had previously been treated with biologics, which the clinical adviser to the ERG felt was reflective of clinical practice. Further information regarding the individual biologic therapies taken by subjects who reported previously taking biologics was provided in response to clarification. The most commonly used in the tildrakizumab 100mg, tildrakizumab 200mg and placebo arm was etanercept [redacted]% and [redacted] respectively, followed by adalimumab; [redacted] respectively. Information was also provided on the n (%) of patients previously treated with systemic non-biologic therapy in used in the tildrakizumab 100mg, tildrakizumab 200mg and placebo arm; [redacted] respectively. In clinical practice, these proportions would be expected to be notably higher, where all patients are expected to receive systematic non-biologic therapy prior to commencing biologic treatment options.

4.2.3.2 Summary of efficacy results in reSURFACE1

Clinical efficacy data for reSURFACE1 are presented in section B.2.6 of the CS. These efficacy data are based on the FAS with non-responder imputation (as most appropriate) and are summarised along with the quality of life measure DLQI and EQ5D in Table 3. The outcome EQ5D, whilst not being a key primary or secondary end-point, was an exploratory end-point and used to inform the economic modelling. For primary outcomes, the proportion of PASI75 and clear or minimal PGA responders, and key secondary endpoints PASI90 and PASI100, tildrakizumab 100mg and 200mg performed statistically significantly better than placebo at 12 weeks. Results for additional secondary end-points were detailed in the clinical study report for reSURFACE1. DLQI was reported as a quality of life outcome in CS Section B.2.6.7: at Week 12, the proportions of subjects with DLQI score of 0 or 1 was statistically greater in the tildrakizumab groups compared with the placebo group. Additional data for DLQI change from baseline at 12 weeks was provided in the clarification response from the company. Pairwise comparisons showed that tildrakizumab 100mg and 200mg performed statistically significantly better than placebo at 12 weeks. Change from baseline in EQ5D at weeks 12 and 28 scores, provided in response to clarification, remained consistent in the tildrakizumab 100mg and 200mg arms. No statistical tests were applied to the data collected during the placebo-controlled phase of the trial.

The proportion of responders in each group for these outcome and level of significance for relevant comparisons is detailed in Table 3.

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Table 3. Primary efficacy end-points and key secondary end-points from reSURFACE1 (FAS) at weeks 12 and 28. Adapted from tables 11, 12, 15 and 17 of the CS.

	Week	TIL 100mg	TIL 200mg	Placebo	TIL 100mg vs. placebo (% difference (95% CI; p value)	TIL 200mg vs. placebo (% difference) (95% CI; p value)
PASI 75 Responders, n (%) (Non- responder imputation)	12	197 (63.8%)	192 (62.3%)	9 (5.8%)	58.0% (51.0 to 64.1; p<0.001)	56.6% (49.6 to 62.8; p<0.001)
	28	229 (76.6%)	236 (79.2%)	-	-	-
Clear or minimal PGA Responders, n (%) (Non- responder imputation)	12	179 (57.9%)	182 (59.1%)	11(7.1%)	50.9% (43.6 to 57.4; p<0.001)	52.1% (44.8 to 58.5; p<0.001)
	28	188 (62.9%)	199 (66.8%)	-	-	-
PASI 90 Responders, n (%) (Non- responder imputation)	12	107 (34.6%)	109 (35.4%)	4 (2.6%)	32.1% (25.9 to 38.0; p<0.001)	32.9% (26.8 to 38.8; p<0.001)
	28	147 (49.2%)	170 (57.0%)	-	-	-
PASI 100 Responders, n (%) (Non- responder imputation)	12	43 (13.9%)	43 (14.0%)	2 (1.3%)	12.7% (8.0 to 17.3; p<0.001)	12.7% (8.3 to 17.2; p<0.001)
	28	67 (22.4%)	91 (30.6%)	-	-	-
DLQI score of 0 or 1 Responders, n (%) (no imputation for missing data, treated as missing)	12	126 (41.5)	132 (44.2)	8 (5.3)	36.1 (29.3, 42.5; p <0.001)	38.9 (31.9, 45.4;p <0.001)
	28	[redacted]	[redacted]	-	-	-
Change from baseline in DLQI score, mean (SD)	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ5D change from baseline mean(SD)	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	28	[redacted]	[redacted]			

For patients in the TIL100mg arm and the TIL200mg who continued to receive their same dosing regimen after the placebo-control phase (phase 1), with first dose in phase 2 received at 16 weeks, the proportion of patients responding at 28-weeks is higher than that of 12-weeks, for all efficacy end-points (Table 3). The CS also presents the proportion of patients achieving PASI75 and PGA ‘clear or ‘minimal’ over the duration of phase 1 and 2, with the highest proportion of responders in the tildrakizumab 100mg and tildrakizumab 200mg arms seen at 22 weeks (Figure 3).

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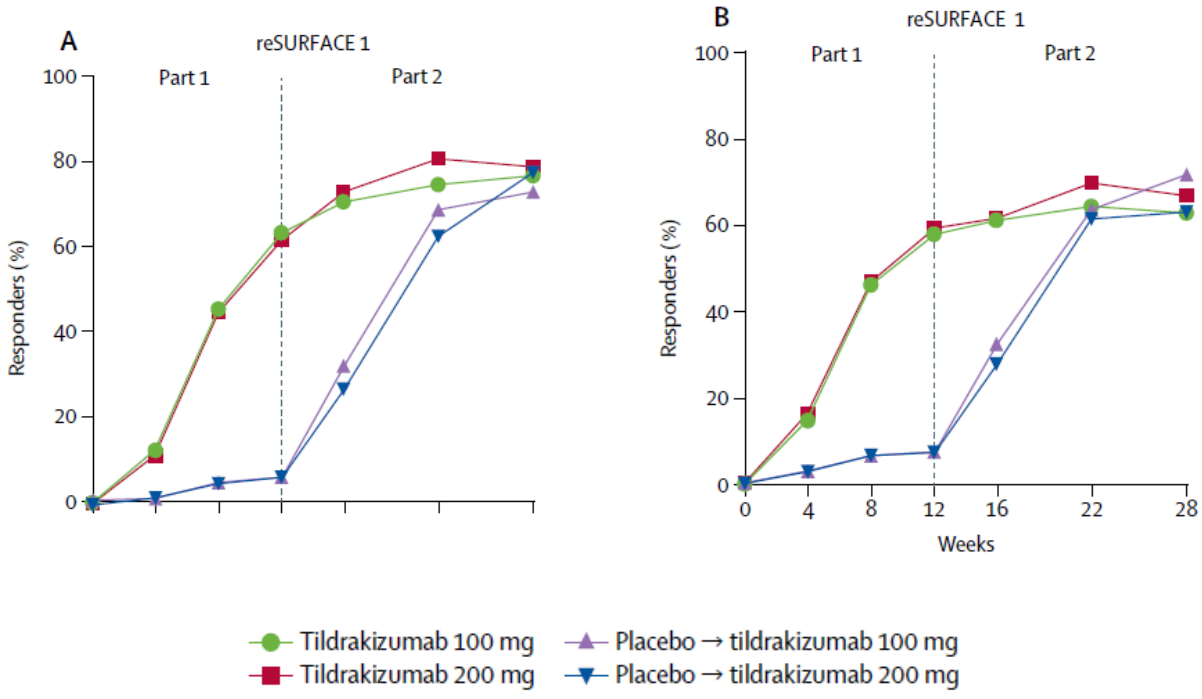

A: Proportion of patients achieving a PASI 75 response; B: Proportion of patients achieving PGA 'clear' or 'minimal' with at least a two-grade reduction. In Part 1, the FAS population included all randomised patients who received one or more dose of study medication; in Part 2, it included all patients who entered Part 2 and received one or more doses of study medication. Presented as NRI data. Abbreviations: NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment. Source: Reich et al 2017.

Figure 3 Proportion of patients achieving a PASI 75 and PGA 'clear' or 'minimal in Parts 1 and 2 of reSURFACE 1 (CS Figure 8, page 48 of the CS)

4.2.4 Results from reSURFACE2

4.2.4.1 Participant flow in reSURFACE2

Participant flow in reSURFACE2 is presented in Appendix D, figure 4. To summarise, 1090 patients were randomised, 1026 (96.1%) of patients completed Part 1 (up to 12 weeks) of the trial (tildrakizumab 200mg 300/314 (95.5%), tildrakizumab 100mg 295/307 (96.1%), placebo 142/156 (91.0%), etanercept 289/313 (92.3%)). Discontinuation in phase one was low in all trial arms.

At 28 weeks patients were assessed for response to treatment with non-responders (those with a PASI <50) discontinued. A total of 1025 patients commenced Part 2(12-28 weeks) of the trial, with 995 patients completing this phase (tildrakizumab 200mg 294/300 (98.0%), tildrakizumab 100mg 289/294

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(98.2%), placebo re-randomised to tildrakizumab 200mg 69/72 (95.8%), placebo re-randomised to tildrakizumab 100mg 66/70 (94.2%) and etanercept 277/289 (95.8%)). In phase two, the proportion of patients discontinuing treatment was low in all trial arms.

Patient baseline characteristics for reSURFACE2 are presented in section B.2.2, Table 8 of the CS. These were similar across trial arms. The trial had a higher proportion of men compared to women in the tildrakizumab 100mg, tildrakizumab 200mg, placebo arm and etanercept arm; 72%, 72% and 71% and 72% respectively. The majority of the participants were white; 91%, 90%, 92% and 92%, respectively. Mean± SD baseline PASI score was 20.5 (7.63), 19.8 (7.52), 20.2 (7.36) and 20 (7.52), respectively. The proportion of patients previously treated with biologics was around half of that in the reSURFACE1 trial, 13%, 12%, 12% and 13% respectively. The ERG note that this may be less than is seen in clinical practice, the clinical adviser to the ERG felt it was unlikely that tildrakizumab would be used a front line therapy after non-biologic treatment and patient will therefore be more likely to have tried another biologic before tildrakizumab. This is likely to become even more so with the advent of adalimumab biosimilar, which, due to price, is likely to become the first biologic used.

Mean(SD) baseline DLQI scores were provided in response to clarification, these score were similar across arms, tildrakizumab 100mg, [redacted] tildrakizumab 200mg [redacted] placebo [redacted] and etanercept, [redacted] Further information regarding the individual biologic therapies taken by subjects who reported previously taking biologics was provided in response to clarification. The most commonly used previous biologic in the tildrakizumab 100mg, tildrakizumab 200mg, placebo and etanercept arm was adalimumab[redacted] respectively. Followed by Infliximab[redacted] respectively. Information was also provided on the n(%) of patients previously treated with systemic non-biologic therapy in used in the tildrakizumab 100mg, tildrakizumab 200mg, placebo and etanercept arm[redacted] respectively. In clinical practice, these proportions would be expected to be higher, as all patients are expected to receive systematic non-biologic therapy prior to commencing biologic treatment options.

4.2.4.2 Summary of efficacy results in reSURFACE2

Clinical efficacy data for reSURFACE2 are presented in section B.2.6 of the CS. These efficacy data are based on the FAS with non-responder imputation (as is most appropriate) and are summarised along with the quality of life measure DLQI in Table 4. In the tildrakizumab 200mg the FAS contains 299 patients and the ITT contains 300 patients. For the co-primary outcome, the proportion of PASI75 tildrakizumab 100mg and 200mg performed statistically significantly better than placebo at 12 weeks and better than etanercept at 12 weeks and 28 weeks. For the co-primary end-point proportion of clear or minimal PGA responders, tildrakizumab 200mg performed statistically significantly better than

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placebo at 12 weeks and better than etanercept at 12 weeks and 28 weeks. Tildrakizumab 100mg performed statistically significantly better than placebo at 12 weeks but not etanercept and at 28 weeks tildrakizumab 100mg performed statistically significantly better than etanercept.

For key secondary endpoints PASI 90 and PASI 100 tildrakizumab 100 and 200mg performed statistically significantly better than placebo at 12 weeks, and etanercept at 12 weeks and 28 weeks. Results for additional secondary end-points were detailed in the clinical study report for reSURFACE2. DLQI was reported as a quality of life outcome in CS Section B.2.6.7: at Week 12, the proportions of subjects with DLQI score of 0 or 1 were statistically significantly greater in the tildrakizumab 100 mg and tildrakizumab 200 mg groups compared with the placebo group. Tildrakizumab 200mg also performed statistically significantly better than etanercept. At 28 weeks, both tildrakizumab 100 and 200mg performed statistically significantly better than etanercept. Additional data for DLQI change from baseline at 12 and 28 weeks was provided in the clarification response from the company. Pairwise comparisons showed that tildrakizumab 100mg and 200mg performed statistically significantly better than placebo and etanercept at 12 weeks and statistically significantly better than etanercept at 28 weeks.

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Table 4 Primary efficacy end-points and key secondary end-points from reSURFACE2 (FAS) at weeks 12 and 28. Adapted from tables 13, 14, 16 and 19 of the CS.

	Week	TIL 100mg	TIL 200mg	Placebo	Etanercept	TIL 100mg vs. placebo (% difference (95% CI; p value)	TIL 200mg vs. placebo (% difference) (95% CI; p value)	TIL 100mg vs. Etanercept (% difference (95% CI; p value)	TIL 200mg vs. Etanercept (% difference (95% CI; p value)
PASI 75 Responders, n (%)	12	188 (61.2%)	206 (65.6%)	9 (5.8%)	151 (48.2%)	55.5% (48.3 to 61.8; p<0.001)	59.8% (52.9 to 65.9; p<0.001)	13.1% (5.3 to 20.7; p=0.001)	17.4% (9.7 to 24.9; p<0.001)
Non- responder imputation	28	216 (73.5%)	217 (72.6%)	-	155 (53.6%)	-	-	20.1% (12.4 to 27.6; p<0.001)	19.2% (11.5 to 26.7; p<0.001)
Clear or minimal PGA Responders, n (%)	12	168 (54.7%)	186 (59.2%)	7 (4.5%)	149 (47.6%)	50.2% (43.2 to 56.5; p<0.001)	54.7% (47.9 to 60.8; p<0.001)	7.3% (-0.5 to 15.0; p=0.0663)	11.7% (4.0 to 19.3; p<0.05)
Non- responder imputation	28	190 (64.6%)	207 (69.2%)	-	131 (45.3%)	-	-	19.6% (11.7 to 27.3; p<0.001)	24.1% (16.2 to 31.7; p<0.001)
PASI 90 Responders, n (%)	12	119 (38.8%)	115 (36.6%)	2 (1.3%)	67 (21.4%)	37.5% (31.1 to 43.4; p<0.001)	35.3% (29.2 to 41.1; p<0.001)	17.4% (10.3 to 24.4; p<0.001)	15.2% (8.3 to 22.1; p<0.001)
Non- responder imputation	28	161 (54.8%)	169 (56.5%)	-	85 (29.4%)	-	-	25.5% (17.6 to 33.0; p<0.001)	27.3% (19.5 to 34.7; p<0.001)
PASI 100 Responders, n (%)	12	38 (12.4%)	37 (11.8%)	0	15 (4.8%)	12.4% (8.5 to 16.6; p<0.001)	11.7% (7.8 to 16.0; p<0.001)	7.6% (3.3 to 12.3; p<0.001)	7.0% (2.8 to 11.6; p=0.001)
Non- responder imputation	28	66 (22.4%)	79 (26.4%)	-	31 (10.7%)	-	-	11.8% (5.9 to 17.9; p<0.001)	15.7% (9.6 to 22.0; p<0.001)
DLQI (Week 12) Responders, n (%) (no imputation for missing data)	12	119 (40.2)	145 (47.4)	1 2 (8 .0)	108 (35.5)	32 .1 (24.5, 39.1; =<0.001)	39.3 (31.8, 46.1; p<0.001)	4.8 (-2.9, 12.5; p=0.221)	11.9 (4.1, 19.5, 0.003)
	28	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Change from baseline in DLQI score, mean (SD)	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	28	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]

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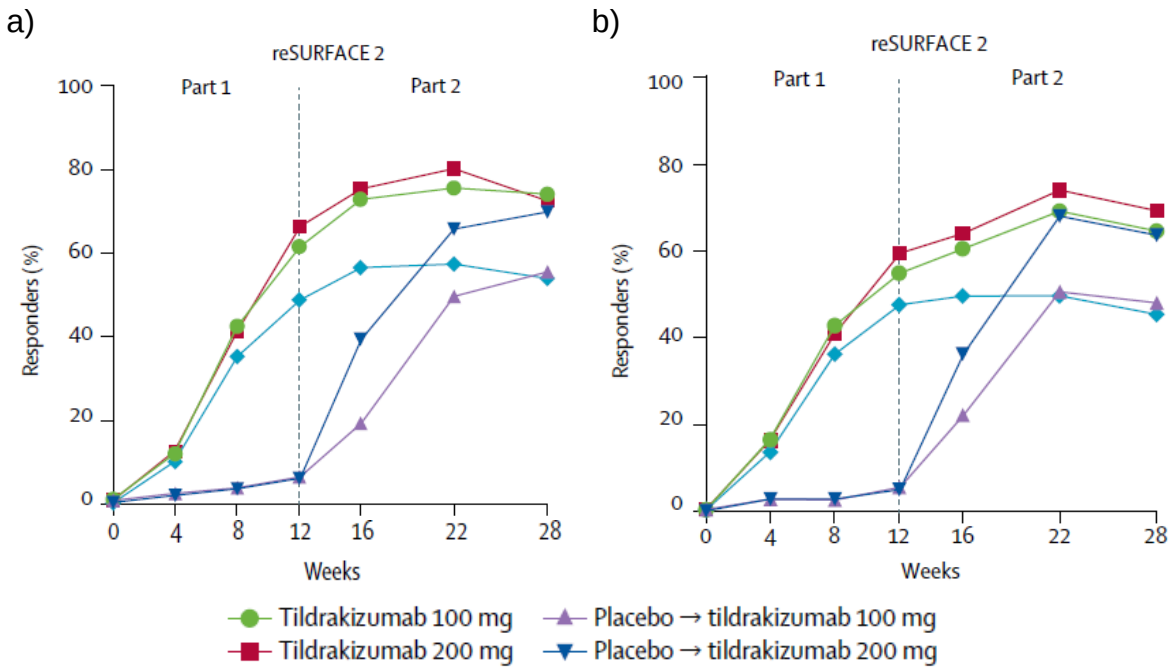
The CS also presents the proportion of patients achieving PASI75 and PGA 'clear or 'minimal over the duration of phase 1 and 2. In the tildrakizumab 100mg and tildrakizumab 200mg arms, the highest proportion of responders seen at 22 weeks (Figure 4).



a) Proportion of patients achieving a PASI 75 response; b) Proportion of patients achieving PGA 'clear' or 'minimal' with at least two-grade reduction. In Part 1, the FAS population included all randomised patients who received one or more dose of study medication; in Part 2, it included all patients who entered Part 2 and received one or more doses of study medication. Presented are NRI data. Abbreviations: NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment. Source: Reich et al 2017.

Figure 4 Proportion of patients achieving a PASI 75 response and PGA 'clear' or 'minimal' in Parts 1 and 2 of reSURFACE 2 (Figure 9 of the CS)

4.2.5 Comments on generalisability of the reSURFACE trials

The ERG note that as non-responders discontinue treatment within reSURFACE1 and reSURFACE2 trials after part 2, i.e. at 28 weeks, the proportion of patients discontinuing treatment during part 3 of the studies is not likely to be reflective those discontinuing treatment clinical practice at these later time-points. This will later be discussed in section 4.2.9.

The ERG note the proportion of patients previously treated with biologic therapy before commencing treatment with tildrakizumab, may not be reflective of clinical practice. The clinical adviser to the ERG felt it was unlikely that tildrakizumab would be used a front line therapy after non-biologic

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treatment and therefore it is possible that a higher proportion of patients will have been exposed to another biologic before commencing treatment with tildrakizumab.

In the company's response to clarification the number and proportion of patients previously treated with a systemic non-biologic therapy at baseline were provided for both trials. These figures were them amended by the company during the factual accuracy check of the ERG report. The ERG note these are lower (total across arms in reSURFACE1 and reSURFACE2, [redacted] than would be seen in clinical practice, where all patients are expected to receive systematic non-biologic therapy prior to commencing biologic treatment options.

The ERG note also note that whilst concomitant medications were not permitted within the trial, due to potential confounding of efficacy end-points, in clinical practice it would not be uncommon for patients to use concomitant medications, such as topical treatments or photo-therapy, especially during times of 'flare-up' of PsA.

4.2.6 Stopping rule – best time point for assessment of efficacy

The ERG requested further information to inform the question of the best time point for a stopping rule for tildrakizumab. They requested for reSURFACE1 and reSURFACE2 PASI 50, PASI 75, PASI 90 and PASI 100 at week 28 for the following subgroups:

- subjects with at least a PASI 75 response at week 12
- subjects with a PASI <50 response at week 12
- subjects with a PASI 50-74 response at week 12.

The results are presented in the company's clarification response Tables 11 to 16. The results for the pooled data with non-responder imputation for patients who remained on their randomised dose of tildrakizumab are presented in Table 5.

Table 5 Response at week 28 conditional on response at week 12 (Pooled resurface 1 and 2 data) (adapted from clarification response Table 16)

	% achieving PASI 75 at week 28					
	TIL 100 mg (n=593)		TIL 200mg (597)		ETN 50mg (n=289)	
	YES	NO	YES	NO	YES	NO
PASI<50 week12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50-75 week12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]

The clinical adviser to the ERG commented that clinical experience with ustekinumab suggests 16 or 20 weeks is a better point for assessment; ustekinumab is also administered every 12 weeks.

4.2.7 Subgroup analysis – Data from reSURFACE1 and reSURFACE2

Pre-planned subgroup analyses for previous exposure to biologic therapy for psoriasis and body weight (baseline weight ≤90kg and >90kg) were conducted. In addition post-hoc subgroup analyses were conducted for previous use of phototherapy and systemic non-biological therapy, and severity of psoriasis assessed in patients with a baseline PASI <20 and ≥20. These were conducted using pooled efficacy data from reSURFACE1 and reSURFACE2. The numbers of patients in each of the subgroups was provided in the company's clarification response (Tables 17 to 40); these are summarised in Table 6.

Table 6 Number of patients in pre-planned and post-hoc subgroup analyses (calculated by ERG from clarification response)

Subgroup		12 week time point			
		Placebo (n)	tildrakizumab 100mg (n)	tildrakizumab 200mg (n)	Etanercept 50mg (n)
Previous use of biologic therapy	No	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]
Weight group	<=90kg	[redacted]	[redacted]	[redacted]	[redacted]
	>90kg	[redacted]	[redacted]	[redacted]	[redacted]
Previous use of phototherapy and systemic non-biological therapy	Yes	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI	<20	[redacted]	[redacted]	[redacted]	[redacted]
	>=20	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup		28 week time point			
		Placebo (n)	tildrakizumab 100mg (n)	tildrakizumab 200mg (n)	Etanercept 50mg (n)
Previous use of biologic therapy	Yes	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]
Weight group	<=90kg	[redacted]	[redacted]	[redacted]	[redacted]
	>90kg	[redacted]	[redacted]	[redacted]	[redacted]
Previous use of phototherapy and systemic non-biological therapy	Yes	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI	<20	[redacted]	[redacted]	[redacted]	[redacted]
	>=20	[redacted]	[redacted]	[redacted]	[redacted]

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The ERG notes that the subgroup by previous non-biologic systemic agent also includes phototherapy. The proportion of patients in the subgroup who had received this therapy is high: 69% in the 100mg dose group and 67% in the 200mg dose group. This contrasts with the smaller proportion of patients who received a previous non-biologic systemic agent in the trials (see Sections 4.2.3.1 and 4.2.4.1) suggesting this subgroup represents mainly those who received previous phototherapy.

4.2.7.1 Subgroup analysis of reSURFACE trials' data at 12 weeks

Subgroup results from the reSURFACE trials for outcomes PGA 'clear or minimal', PASI 75, PASI 90 and PASI 100 at week 12 results were presented as forest plots in Appendix E of the CS. The results for PASI 75 with the 100mg dose (being the primary outcome and dose in the economic model) is shown in Figure 5.

Figure 5 Forest plot for PASI 75 response for tildrakizumab 100mg versus placebo at Week 12 by subgroup (CS Appendix E Table 17)

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With both doses there was little impact of the previous use of biologics. With the 100 mg dose there is a suggestion of a higher response rate in patients weighing no more than 90kg than in heavier patients and this effect was also seen for the 200mg dose for PASI 90. However, the trials were not powered to detect differences between dose regimens. There was also a suggestion of an effect of baseline PASI, with patients < 20 responding slightly better than those with higher PASI; this effect was most obvious for PGA 0/1. No formal statistical tests of interaction were reported in the CS or clarification response.

4.2.7.2 Subgroup analysis of reSURFACE trials' data at 28 weeks

Subgroup analysis of 28 week data from the resurface trials were presented in the CS, section B.2.7: for the subgroups body weight (baseline weight ≤90kg and >90kg) and patients with a baseline PASI <20 and ≥20 results for the outcomes PASI 75, PASI 90, PASI 100 and PGA of 'clear' or 'minimal' at 28 weeks were presented. The results were presented as histograms to compare the effect of the two doses of tildrakizumab, rather than subgroup effects. The CS states that the results (see CS Figures 16 and 17) show a trend for better outcomes at 28 weeks in patients with a PASI ≥20 or body weight >90kg treated with 200mg dose compared to a 100mg dose. The CS acknowledges that the resurface trials were not designed or powered to detect potential differences between the two doses of tildrakizumab. The ERG does not find the evidence of a better response with the 200 mg dose in patients weighing >90kg convincing noting that similar differences between the doses was seen in patients ≤90kg. For patients with a baseline PASI >20 the evidence for a better response with the 200mg dose (at week 28) is stronger: the proportion of patients achieving PASI 90 with 100mg vs 200mg was 46.6%, 57.7% ($p<0.05$),; and the proportion of patients achieving PASI 100 with 100mg vs 200mg was 15.5%, 28.6%, ($p<0.05$).

Regarding subgroup effects (ignoring differences between treatment doses) the ERG notes that the subgroup analysis results indicate that patients weighing >90kg or with baseline PASI ≥20 on average respond less well but the differences are not great and without confidence intervals it is difficult to draw conclusions. The ERG requested the subgroup analyses at week 28 for the subgroups of patients with 'previous use of biological therapy' and patients with 'previous use of phototherapy and systemic non-biological therapy', which had not been included in the CS. These were provided as tabulated data with no confidence intervals (see clarification response (Tables 29 to 40)). The results are presented in Table 7. The analysis shows that on average there is a lower level of response in patients who had previous use of biological therapy compared with those who had not, although without confidence intervals it is difficult to draw firm conclusions. There was no apparent effect of previous use of phototherapy and systemic non-biological therapy.

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Table 7: Subgroup analysis of week 28 data - Percentage of patients who achieved outcome (adapted from Clarification response Tables 29, 32, 35 and 38)

		PASI 75	PASI 90	PASI 100	PGA0/1
100mg					
Previous use of biological therapy	No	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]
Previous use of phototherapy and systemic non-biological therapy	No	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]
200mg					
Previous use of biological therapy	No	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]
Previous use of phototherapy and systemic non-biological therapy	No	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]

4.2.8 Phase IIb trial

The phase IIb, randomised, double-blind, placebo-controlled trial [7] was conducted to evaluate the safety and efficacy of subcutaneous tildrakizumab in patients with moderate-to-severe chronic plaque psoriasis. The details are summarised in Table 8. In contrast to the phase III trials the primary time point is 16 weeks, opposed to 12 weeks.

Table 8 Summary of the Phase IIb trial Adapted from Table 4 of the CS

Study	Papp 2015[7]
Study design	Phase IIb randomised, double-blind, placebo-controlled, 72 week study. Patients were randomised in a 1:2:2:2:1 ratio to one of five treatment arms. The study has three parts; week 0-16, weeks 16-52 and weeks 52-72.
Population	355 patients, Men and women aged ≥ 18 years old with predominantly plaque psoriasis for ≥ 6 months. participants were candidates for phototherapy or systemic therapy; had a Psoriasis Area and Severity Index (PASI) score ≥ 12; psoriasis body surface area involvement ≥ 10%; and a Physician's Global Assessment (PGA) of moderate, marked or severe at baseline.
Intervention(s)	tildrakizumab (5mg, 25mg, 100mg or 200mg via subcutaneous injection)
Comparator(s)	Placebo.
Outcomes assessed in the trials and relevant to the decsion problem	Primary efficacy end point: The proportion of participants with a reduction in PASI score of ≥ 75% from baseline at week 16. Secondary end points (in part I) : PASI 75 at week 12 The proportion of participants with a PGA status of 'cleared' or 'minimal' at week 16, PASI 90 at week 16, Time to PASI 75 Mean change from baseline in the Dermatology Life Quality Index (DLQI) at week 16. Secondary end points (part II):

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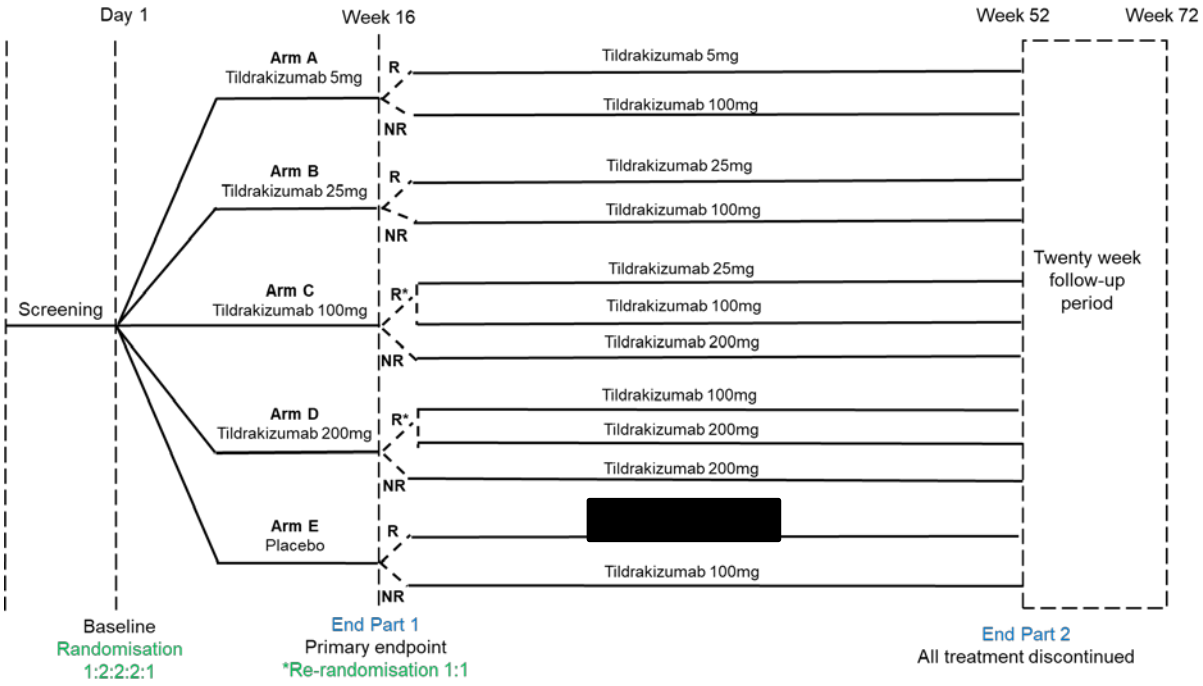
	PASI 75 at week 52 (grouped by PASI 75 status at week 16) PGA status of 'clear' or 'minimal' at week 52. Secondary end-points (Part III): Relapse was assessed as the time that week 52 improvement from baseline was reduced by > 50% (in participants who attained PASI 75 at week 52).

In response to clarification, the company provided addition detail regarding the study design of the phase IIb trial. During phase 1 (weeks 0-16), participants were randomized to receive subcutaneous tildrakizumab (5, 25, 100, 200 mg) or placebo at weeks 0 and 4. During phase 2 (16-52 weeks), all participants received active treatment. Treatment allocation was based on responder status, those who achieved ≥75% improvement in PASI response from baseline were considered responders. Phase 3 (weeks 52-72) consisted of a 20 week follow-up period (Figure 6).



Randomised participants were stratified by baseline weight (≤90 kg, >90 kg) and prior exposure to biological therapy for psoriasis (yes/no). NR: non-responders who achieved <50% improvement in PASI response from baseline); R: responders who achieved ≥75% improvement in PASI response from baseline. * Responders in Arm C and Arm D were re-randomised at Week 16 to continue on the same or a reduced dose (100mg tildrakizumab reduced to 25mg and 200mg tildrakizumab reduced to 100mg) every 12 weeks up to Week 52. Subjects who discontinued due to lack of efficacy or loss of response or who took prohibited medications during the first 16 weeks were treated as PASI 75 non-responders and were analysed by carrying over the last post-baseline non-missing PASI score prior to Week 16. Adapted from Papp et al 2015 and the clinical study report (CSR) for the Phase IIb dose finding study

Figure 6 Phase IIb dose finding study of tildrakizumab: trial design, provided in the company clarification letter

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4.2.8.1 Participant flow in Phase IIb trial

A consort diagram provided in CS Appendix D.5 provides full detail on the number of participants entering and completing the study. Discontinuation within the study was generally low with 355 patients being initially randomised a 1:2:2:2:1 ratio to one of five treatment arms. Of these, 339 patients completed the placebo-control phase of the trial (phase I) (95.5%). Patients were then allocated to treatment arms based on responder status with responders initially being re-randomized to 100 mg or 200 mg tildrakizumab. Of those commencing phase two, 292/339 (86.1%) of patients completed. At week 52, participants discontinued treatment and entered a 20-week follow-up period (part III, weeks 52-72), here 266/289 (92.0%) of patients completed.

In response to clarification the company provided a table of baseline characteristics of subjects across treatment arms. Baseline demographic data were generally balanced between the treatment arms. In the licenced dose, TIL 100mg and TIL 200mg arms, the majority of patients were white 82% and 85%, respectively and male, 85% and 76%, respectively. The majority of patients in these arms were overweight or obese with a BMI of over 25, 76% and 75% respectively. In addition, in the licence dose arms, 17% and 22%, respectively, had received prior biologic therapy and 17% and 17%, respectively had been previously treated with a TNF inhibitor therapy.

4.2.8.2 Quality assessment

The quality assessment was informed by the NICE quality assessment questions, the results of which are presented in Appendix D.5 of the CS. The ERG broadly agree with the quality assessment conducted by the company Table 9 with comments informed primarily from the study publication.[7] Information on data management with regards to patient withdrawal was provided in the company's response to clarification.

Table 9 Quality assessment of the Phase IIb clinical trial - adapted from Table 5 Appendix D.5

Quality assessment criterion	Phase IIb study	ERG comment
Was the randomisation method adequate?	Yes	Yes- Randomization of treatment was done centrally by means of an interactive web response system.
Was the allocation adequately concealed?	Yes	Yes- Allocation was done centrally by means of an interactive web response system.
Were the groups similar at the outset of the study in terms of prognostic factors?	Unclear	Yes- Baseline characteristics appear equal across treatment arms in P et al. 2015. – with the exception of ethnicty (white)
Were the care providers, participants and outcomes assessors blind to treatment allocation? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Yes- All study personnel and participants remained blinded to study medication assignment, with the exception of the preparer of the stud medication and the unblinded drug accountability monitor (these individuals were not involved in efficacy or safety assessments).

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Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No- Discontinuation was generally low in across treatment arms.
Is there any evidence to suggest that that the authors measured more outcomes than they reported?	No	No- Results for key end-points reported in Papp et al 2015.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No	The last non-missing post-baseline PASI value obtained in Parts I and was carried forward for any subject who missed the end point assessm and who had not discontinued treatment owing to lack of efficacy, los response, or had used prohibited medications in the corresponding pa the study. Subjects who discontinued prior to Week 16 due to lack of efficacy, of response, or use of prohibited medication were considered not to h achieved PASI 75; those with a missing PASI score at Week 16 were analysed by carrying over the last post-baseline non-missing PASI sc
Also consider whether the authors of the study publication declared any conflicts of interest	Yes	Conflict of interests are declared in Papp et al. 2015 [7]

4.2.8.3 Summary of efficacy results for licenced doses (TIL 100mg and TIL 200mg) of the phase IIb trial

The primary efficacy end point was the proportion of participants with a reduction in PASI score of ≥75% from baseline at week 16. PASI 75 response rates at week 16 were 66% and 74% for the tildrakizumab 100mg and 200mg groups, respectively, compared with 4% for placebo (P <0. 001 for each treatment group vs. placebo). During the placebo-controlled phase of the trial, the highest level of efficacy for PASI 75 response rate (%), for tildrakizumab 100mg and 200mg is seen at 16 week. In the CS it is unclear why a primary time point of 12 weeks is used in the phase III trials. Results for all other efficacy end-points are summarised in Table 10.

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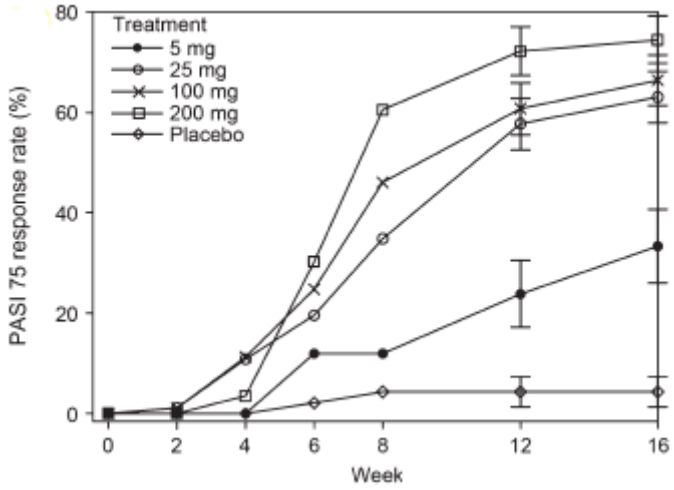

Figure 7 Psoriasis area and severity index (PASI) 75 over time during the placebo-controlled phase 1 (Weeks 0-16). Adapted from Papp et al. 2015.

Table 10 Summary of efficacy endpoints for phase 1, placebo-controlled phase of the phase IIb trial, adapted from Papp et al. 2015 (licenced doses only)

	TIL 100mg (n=89)	TIL200mg (n=86)
PASI 75 responders at week 16 n (%)	59 (66)	64 (74)
PASI 75 responders at week 12 n (%)	54 (61)	62 (72)
PGA response rate (cleared or minimal) n (%)	55 (62)	64 (74)
PASI 90 responders at week 16 n (%)	34/88 (39)	44/84 (52)
Median time (days) to PASI 75 (95% CI)	84 (57-86)	57 (56-64)
Mean change from baseline in DLQI (95% CI)	-8.5 (-9.9—7.1)	-8.8 (-10.3—7.4)
DLQI score of 0 or 1 at week 16 n (%)	46 (52)	48 (57)
≥5-point reduction in DLQI score at week 16 n (%)	57 (65)	61 (73)

PASI 75,≥75% reduction in Psoriasis Areaand Severity Index score; PASI 90,≥90% reduction in Psoriasis Area and Severity Index score; PGA, Physician's Global Assessment; DLQI, Dermatology Life Quality Index.

4.2.8.4 Summary of safety results of the phase IIb trial

Results from the safety evaluation were reported in Appendix F. The overall incidence of AEs was generally similar for all treatment arms and did not differ from placebo. In Part 2, between 54% and 69% of subjects reported at least one AE. Discontinuation due to AEs was low during Part 1 of the study and was consistent across groups. Of 289 subjects who entered Part 3 of the study following completion of Parts 1 and 2, 40% reported at least one AE. The most frequent AEs in Parts 1, 2 and 3 of the study were nasopharyngitis and headache, which occurred with similar frequency in all treatment groups. Frequency of hypertension was found to be dose related, with 9/308 patients experiencing the AE who received tildrakizumab and 0/45 experiencing the AE who received

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placebo. AEs that were assessed as possibly related to tildrakizumab included bacterial arthritis and lymphoedema (part I); and melanoma, stroke, epiglottitis and knee infection (part II). Treatment effects achieved during phase I of the trial, were maintained through 52 weeks of treatment with doses of 100 and 200 mg tildrakizumab.

Table 11. Summary of the number of adverse events occurring during phase I and II. Adapted from Table 22, Appendix F.2

Part one of the study (0-16 weeks)					
	Tildrakizumab 5mg (N=42)	**Tildrakizumab 25mg (n=91)**	**Tildrakizumab 100mg (N=89)**	**Tildrakizumab 200mg (N=86)**	**Placebo (N=45)**
One or more AEs	30 (71)	56 (61)	58 (65)	54 (63)	31 (69)
Drug-related AEs	13 (31)	24 (26)	22 (25)	17 (20)	10 (22)
Serious AEs	0	1 (1)	1 (1)	2 (2)	0
Deaths	0	0	1 (1)	0	0
Discontinuation due to AEs	1 (2)	2 (2)	1 (1)	1 (1)	1 (1)
Part 2 of the study (Weeks 16 to 52)					
	Tildrakizumab 5mg (N=13)	**Tildrakizumab 25mg (n=94)**	**Tildrakizumab 100mg (N=153)**	**Tildrakizumab 200mg (N=79)**	**Placebo**
One or more AEs	7 (54)	60 (64)	105 (69)	52 (66)	NA
Drug-related AEs	1 (8)	23 (24)	32 (21)	19 (24)	NA
Serious AEs	0	5 (5)	6 (4)	3 (4)	NA
***Discontinuation due to AEs**	0	5 (5)	5 (3)	3 (4)	NA

4.2.9 Longer-term clinical effectiveness

Data on the longer term effectiveness of tildrakizumab was presented in the CS - section B2.6.5 (covering 'Part 3' of the trials, i.e. up to week 52 or week 64) and section B2.6.6 (covering the long-term extension from week 64 to week 148).

Results from the longer-term phases of trials should generally be viewed with much more caution than those from the earlier randomised phases because the methods used are usually more prone to biases. The ERG also notes that the primary objective of the long-term extension study was to assess safety/tolerability (p30 of the CS). Although patient flow (CONSORT) diagrams were presented in the CS for Parts 1 and 2 of the reSURFACE trials there were no such data for Parts 3 and the long-term extension phases. The ERG requested these data to clarify the numbers of patients who were

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withdrawing from the studies at each stage, and the numbers entering each phase as 'partial responders' (≥50% but <75% PASI improvement from baseline) or 'responders' (≥75% PASI improvement). These are presented in Table 12 but the ERG notes that they are limited in detail e.g. no data were presented on the number of patients withdrawing in these later study phases due to adverse events.

'Part 3' of the trials

It is important to note that the results presented for Part 3 relate to patients who responded to tildrakizumab at week 28. Patients who had been on tildrakizumab up to week 28, but who were non-responders at week 28 (i.e. <50% improvement in PASI from baseline), had their treatment stopped and so did not enter Part 3. As such the results presented in the CS relate to a more selective 'observed' population rather than a more inclusive population (e.g. intention to treat). A further limitation of the longer-term results data is that comparisons with etanercept (in reSURFACE 2) were not available. This is because the trial design and protocol specified that patients who were responders to etanercept at week 28 had to stop their trial treatment.

The CS presented Part 3 results for patients randomised to tildrakizumab in Part 1 who continued on the same dose throughout Part 3. Data were presented in Figures 10 and 11 in the CS along with corresponding results for the physician's global assessment (PGA) outcome. The CS states that, of the PASI 75 responders at week 28 in reSURFACE 1 98 of 112 (87.5%) on tildrakizumab 100mg and 107 of 114 (94%) on tildrakizumab 200mg had a PASI 75 response at week 64. Lower response rates were seen for PGA at week 64: [redacted] for tildrakizumab 100mg and [redacted] for tildrakizumab 200mg. For patients on tildrakizumab 100mg and 200mg who had a PASI 75 response at Week 28, a PASI 90 response was seen in [redacted] of patients at Week 64. Corresponding data on the same outcomes were also presented in the CS for the reSURFACE 2 trial, up to week 52, with the response rates being similar to those seen in reSURFACE 1. However the ERG notes that the number of responders (PASI 75) stated here does not match the numbers reported in Table 1.

Long-term extension studies

The 'long-term extension' studies described in the CS covered the periods from 64 weeks in reSURFACE 1, and 52 weeks in reSURFACE 2, through to 148 weeks and included patients who had at least a PASI 50 response in Part 3. These patients received the same dose of tildrakizumab (100mg or 200mg every 12 weeks) as they were receiving on completion of Part 3 of the study. Unlike the Part 3 results - which were presented separately for each trial - pooled data from the two reSURFACE trials were presented in the CS for the long-term extension phase. The CS stated that [redacted] of patients on tildrakizumab 100mg (n=[redacted] at week 64) and [redacted] of patients on tildrakizumab 200mg (n=[redacted] at

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week 64) were PASI 75 responders at week 112, with responses maintained at week 148. Corresponding data were also presented for PASI 90 (see Figures 14 and 15, p57 of the CS).

The proportion of patients who entered Part 3 of the trials (at week 28) but did not enter the long-term extension study (at week 64) was [redacted] for 100mg and 200mg groups respectively in the reSURFACE 1 trial. For reSURFACE 2 the figures are lower and are different for the 100mg and 200mg groups being [redacted] respectively (Table 12). It is unclear why these data differ notably across the two trials.

Table 12 Patient numbers in Part 3 and the long-term extension phases of reSURFACE 1 and reSURFACE 2

	reSURFACE 1		reSURFACE 2	
	Tild 100mg in Part 1	Tild 200mg in Part 1	Tild 100mg in Part 1	Tild 200mg in Part 1
Patients in population Part 2 (all randomised subjects)	[redacted]	[redacted]	[redacted]	[redacted]
Completed Part 2 (Week 28)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued at Week 28 due to non-response	[redacted]	[redacted]	[redacted]	[redacted]
-Non completed Part 2 due to lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
Patients in population Part 3 (Full Analyses Sets)	[redacted]	[redacted]	[redacted]	[redacted]
Entered Part 3 as responders	[redacted]	[redacted]	[redacted]	[redacted]
Entered Part 3 as partial responders	[redacted]	[redacted]	[redacted]	[redacted]
Received at least one dose of study medication in Part 3	[redacted]	[redacted]	[redacted]	[redacted]
Entered the long-term extension study	[redacted]	[redacted]	[redacted]	[redacted]
Did not enter the long-term extension study	[redacted]	[redacted]	[redacted]	[redacted]

Tild = Tildrakizumab

The CS utilised registry data on discontinuation rates from both the British Association of Dermatologists Biologic Interventions Register (BADBIR)[8] in the base case and the Danish Biologic Interventions registry (DERMBIO)[9] in scenario 9 (p151 of the CS). However, it is difficult to compare any discontinuation rates derived for tildrakizumab (from data in the CS and from Table 12) with rates for other biologics derived from large registry datasets for the following reasons:

- The lack of detail on reasons for discontinuation (or continuation) of tildrakizumab e.g. reasons for not entering the long-term extension study in Table 12 .

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- Because the treatment continuation/stopping rules and decisions for patients in a clinical trial are often different to real clinical practice. Indeed, the DERMBIO study excluded patients treated as part of a clinical trial.[9]
- The large difference in sample sizes between the newer and more established biologics.

The company's base case used an assumption that all biologics have the same rate of discontinuation (18.7%) based on data used in the brodalumab STA (from BADBIR). It is clear though from the registry studies that different rates of discontinuation exist across biologics. The DERMBIO study (of infliximab, etanercept, adalimumab, ustekinumab and secukinumab) reported ustekinumab as having the highest rate of drug survival and secukinumab the lowest rate, although the secukinumab group had the lowest proportion of biologic-naive patients.

In the CS, scenario analysis 9 (p151 of CS) used alternative discontinuation data. The most optimistic data from DERMBIO (i.e. the rates for ustekinumab) were used to estimate a discontinuation rate for the newer biologics, since there are limited data available for the newer biologics (i.e. tildrakizumab, ixekizumab, brodalumab, and guselkumab). This was done on the basis that the newer biologics are all IL-inhibitors - the same as secukinumab and ustekinumab. However, the difference in discontinuation rates between secukinumab and ustekinumab suggest that this assumption is subject to uncertainty.

The CS did not make use of the UK-specific registry data (BADBIR) on the basis of its shorter time horizon and the lack of data on secukinumab. However, as discussed above, the company did not end up using the DEMBIO secukinumab data in the CS, assuming instead that secukinumab had the same discontinuation rate as ustekinumab.

The ERG also requested information on whether any stopping rules were applied to both Part 3 and the long-term follow up phases. This was to clarify whether tildrakizumab must be discontinued in the event of non-response, or whether patients were permitted to continue taking tildrakizumab in the hope of regaining a response. In clinical practice non-responders would likely be switched to another biologic. However, the company did not clarify the ERG's concerns on this issue, as its response related to the eligibility criteria for entering these study phases, rather than to stopping criteria once a patient was within a particular phase.

4.2.10 Adverse events

Adverse events data were reported on pages 77-83 of the CS. Data were presented for each of the two randomised phase III reSURFACE trials and also for a pooled analysis comprising of the two phase III trials plus the phase IIb randomised dose-finding trial. The pooled analysis included 2,081 patients:

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705 for tildrakizumab 100mg, 708 for tildrakizumab 200mg, 355 for placebo and 313 for etanercept.[10]

Adverse events in Part 1 of the trials

'Part 1' of the trials covered the placebo phases which were up to week 12 for the two reSURFACE trials and up to week 16 for the phase IIb trial. In the pooled analysis, incidence of treatment emergent adverse events (TEAEs: range 47.9% to 54.0%); serious TEAEs (range 1.4% to 2.3%); discontinuations due to AEs (range 0.6% to 1.9%) and severe infections (range 0.0% to 0.3%) were comparable across all four trial interventions (see Table 22 of the CS).

The submitted data for the individual trials indicated that the most frequent adverse event up to week 12 was nasopharyngitis. In reSURFACE 1 the incidence of nasopharyngitis ranged between 5% (in the placebo group) and 8% (in the tildrakizumab 100mg group). The incidence of nasopharyngitis was a little higher in reSURFACE 2 than in reSURFACE 1; patients taking tildrakizumab had rates of 13% (100mg) and 11% (200mg) which was similar to etanercept (12%), though higher than placebo (8%). In reSURFACE 2 injection site reactions were more frequent in patients taking etanercept (5%) compared to those receiving tildrakizumab 100mg (<1%), tildrakizumab 200mg (1%) and placebo (1%).

The EMA summary of product characteristics (SmPC) document for tildrakizumab states that headache, gastroenteritis, nausea, diarrhoea, injection site pain, and back pain were among the most common adverse reactions. Examination of the reSURFACE 1 and reSURFACE 2 clinical study reports showed the incidence of these events to be very low (most were below 2%) with little, if any, differences in rates across trial groups.

Adverse events in the full trial periods

The 'full trial period' covered up to week 52 for the phase IIb trial and reSURFACE 2 and up to week 64 for reSURFACE 1. Results were reported as exposure-adjusted rates (patients per 100 patient-years). Exposure-adjusted rates for TEAEs were 77.0 and 79.3 for tildrakizumab 100mg and tildrakizumab 200mg respectively but were notably higher (see Table 22 of the CS) for placebo (153.5) and etanercept 50mg (148.6). Differences were also apparent for treatment-related AEs.

No explanation was offered in the CS as to why the *treatment* emergent adverse event rates for placebo should be so much higher than both the 100mg and 200mg tildrakizumab groups - results which do not seem clinically plausible. The lack of credibility of these results must also cast doubt on the reliability of the full trial period results for the comparisons of tildrakizumab with etanercept. Exposure-adjusted rates are valid statistics for treatment comparisons when a specific event rate is

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fairly constant over time. Treatment comparisons may be biased for events that usually occur early in a study, events whose incidence rates decrease over time, or events that occur on a delayed basis.[11] Such biases may explain these unusual results reported in the CS. Moreover, there was variation across treatment groups in the durations over which adverse events were assessed (e.g. placebo assessment stopped at week 12 in the reSURFACE trials) and consequently in the total exposure times: 998 patient-years for tildrakizumab 100 mg, 929 patient-years for tildrakizumab 200 mg, 219 patient-years for placebo and 153 patient-years for etanercept.[10]

There were seven deaths across the studies up to week 64 with none considered to be treatment-related. One suicide attempt was reported in a patient taking tildrakizumab 200mg but this event was considered not to be related to study treatment.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The NMA presented compares the efficacy of tildrakizumab (100 mg and 200 mg) with the therapies adalimumab, apremilast, brodalumab etanercept, ixekizumab, risankizumab, guselkumab, secukinumab, ustekinumab and DMF.

As noted earlier in the description of the related systematic review, in terms of comparators, the NMA neither adheres to the NICE scope, nor the company's decision problem, nor does it include all relevant comparators (irrespective of licensing or NICE recommendations) - which can be considered methodologically desirable.

The methods of the review to identify and select studies for inclusion in the NMA have been discussed in Section 4.1. A PRISMA flow diagram is presented as Figure 18 of the CS, along with a table of the included trials (CS Table 21). The excluded studies with reasons for exclusion are listed in CS Appendix D, Table 10. The results of the quality assessment (presented in Table 20, Appendix D .11 of the CS) suggest that overall, the quality of most studies was acceptable: although many items were recorded as unclear and the CS did not report actual risk of bias judgements either for individual domains nor overall judgements, the ERG assessment is that very few indicated a high risk of bias.

The ERG did not undertake independent searches to check that all relevant studies were included in the NMA, owing to time constraints. However, a comparison of studies included in this STA with the most recent STA in moderate to severe plaque psoriasis (of brodalumab) was undertaken. In addition a comparison was made with the review of immunomodulators recently published by the Institute for Clinical and Economic Review (ICER), this being the most recent of a number of NMAs for immunomodulating therapies for moderate to severe psoriasis conducted in recent years (published August 2018).[12] It should be noted that comparing NMAs can be difficult as the treatments included

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vary depending upon the date (and hence treatments and data available) and also the scope of the analysis. The ICER NMA is (as far as the ERG is aware) the most inclusive NMA available in terms of included treatments: included treatments are adalimumab, apremilast, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab and ustekinumab. The brodalumab STA NMA included fewer treatments being an earlier analysis, but did include DMF.

The ICER NMA was restricted to Phase III trials. Compared with the ICER NMA more trials were included in the tildrakizumab NMA because it was not restricted to Phase III trials. However, based on this comparison some Phase III trials were missing from the tildrakizumab NMA. Four etanercept arms were omitted because they were components of phase III trials of interventions not included in the tildrakizumab NMA.[13-16] One trial appears to have been missed because it was too recent: the CLARITY trial of secukinumab versus ustekinumab was available only in grey literature. The IMMhance trial was excluded as it compared risankizumab with placebo which the company stated was not a comparison of interest in their NMA.[17] Bagel 2012[18] was excluded from the tildrakizumab NMA because the psoriasis had to have scalp involvement, and the IXORA-S trial of ixekizumab versus ustekinumab was deemed to involve ineligible interventions (Ixekizumab 160mg loading dose then 80mg every 2 weeks for 12 weeks versus ustekinumab by weight).[19]

A number of trials were identified for the Brodalumab NMA that were not included in the tildrakizumab NMA. Some of these were of infliximab.[16, 20-26] Others included etanercept arms but the main comparator was not included in the review.[13-15] Two of different doses of the treatment of interest only, with no placebo or other comparator: secukinumab[27] and etanercept.[28] Two were of etanercept in combination with other active treatments.[29, 30] One trial of adalimumab did not include placebo or a relevant comparator.[31] The ERG considers that the omission of all these trials is reasonable according to acceptable inclusion criteria

These comparisons demonstrate the difficulty of conducting appropriate NMAs and of comparing them. Overall, the review and study selection as conducted for the tildrakizumab NMA is based on reasonable criteria and study selection; only the decision to exclude infliximab appears to be not well justified given that its trials are not restricted to any sub-group of moderate to severe patients and the licence for tildrakizumab 100mg does not proscribe its use in very severe patients.

The tildrakizumab NMA included all doses of the treatments in order to strengthen the network: included trials were of licensed doses of treatments specified in the scope but where the included trials also had arms of unlicensed doses, these were also included in the network. If an inclusive approach (rather than restricting the network to licensed doses of the treatments in the company scope) was to

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be adopted then all treatments and all doses studied should have been included. Instead this approach for the tildrakizumab NMA was used inconsistently, with the omission of trials that did not include the licensed dose in one arm, and in the omission of infliximab (and it could also be argued certolizumab pegol) but the inclusion of some trials of risankizumab. In summary, the ERG considers the main problem with the NMA is the omission of infliximab trials: in their clarification questions the ERG requested that the NMA be re-run to include infliximab.

The base-case NMA includes both licensed doses of the therapies specified in the scope and unlicensed dose arms from the identified trials. All drug's different doses and/or dosing regimens were treated as unique comparators except for etanercept where 25 mg twice weekly and 50 mg once weekly were merged. Sensitivity analyses are discussed in section 4.4.

The base case NMA included data from 45 RCTs. The ERG note that this compares with 59 trials included in the NMA for the recent STA of brodalumab (TA511).

The CS stated that treatments not included in the NICE scope were included in the NMA because the NMA was conducted for use on a global basis and so includes a broader base of comparators than was required for this submission; the inclusion of these additional treatments enables a more complete network to be used for the final health economic assessment. As noted earlier, the ERG finds the selection of treatments inconsistent.

The NMA focused on the PASI response rates (PASI 50, PASI 75, PASI 90 and PASI 100) with the results used to inform the economic model.

Two analyses were conducted: one using a 12-16 week time point (Stage I) (using placebo controlled phases of trials); and one using a 24-28 week time point (Stage III) (as 24-28 week data are not placebo controlled; the Stage III network used placebo data from 12-16 weeks). A Stage II analysis of direct comparisons between active treatments only could not be run as there was no connected network. The Stage III network was a reduced network of only 26 trials as not all studies reported data at 24-28 weeks (see Appendix L.6 Figure 38 of CS).

Studies that assessed treatment schedules with a reduced dose after the first 12 to 16 weeks were combined with the relevant treatment node for the 12 to 16 week network but were considered as a separate (variable) node in the 28 week network.

The studies included in the tildrakizumab NMA are summarised in CS Table 21 and described in detail in Appendix D. The network diagram is shown in CS Figure 19. Further details are presented in CS Appendix D: the trials' methods are summarised in CS Appendix D Table 11 and the trials'

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outcomes and results are summarised in CS Appendix D Table 12 and details of the participants' baseline characteristics are shown in CS Appendix D Tables 15, 16 and 17. The trials included in the 12-16 week, 12 week only, and 24-28 week analyses are listed in CS Appendix L.5, Tables 61-63 respectively).

At the clarification stage the ERG questioned the omission of infliximab from the NMA. In their clarification response the company provided a sensitivity analysis including infliximab which enlarged the stage 1 network. The following studies were added:

- Chaudhari et al 2001[24]
- Gottlieb et al 2004[23]
- EXPRESS[25]
- EXPRESS II [25]
- Yang et al 2012[26]
- Torii 2010[21]

The company noted that all of the infliximab trials reported data at 10 weeks rather than 12 or 16 weeks (only Gottlieb 2004 also reported data at 14 weeks but only for PASI 75), and therefore, the sensitivity analysis was conducted using data at 10 weeks for infliximab.

Compared to the NMA in the Brodalumab STA one infliximab trial was missed: a placebo controlled RCT comparing infliximab and etanercept.[16] And an additional trial was included - a randomized comparison of continuous vs. intermittent infliximab maintenance regimens - as this also included a placebo comparison its inclusion was appropriate.[22]

In general, including the additional infliximab trials, patient characteristics were broadly similar across trials.

To test the robustness of the NMA the ERG also asked the company to run sensitivity analyses including only Phase III trials and also to include only licensed doses.

4.3.1 Stage I NMA

The CS stated that the time point selected varied across the studies but that where studies reported results for more than one time point within this range, the time point with the most information was used and, if they reported the same amount of data, the earliest time point was used. To explore the

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impact of using different time points a sensitivity analysis was conducted using only 12 week data. The ERG checked the time points used against those used in the ICER NMA and found some discrepancies (see Appendix Table). Where there were discrepancies, the given trial's primary time point was identified. Regarding the sensitivity analysis including infliximab trials both the sensitivity analysis and the ICER NMA used 10 week data.

Checking of the data time points used in the tildrakizumab NMA showed that for some data points the time point used was not the primary one, nor did it match with the 'usual' time point for that treatment.

- For ustekinumab (and secukinumab) the 12 week time point data were used although the primary trial endpoint was 16 weeks. However, all other trials of these two drugs did use 12 weeks and so this decision can be considered consistent.
- For all the brodalumab trials the primary endpoints are at 12 weeks but for one trial (Papp 2012[33]) the tildrakizumab NMA used 16 week data.
- For all guselkumab trials the primary endpoints are at 16 weeks but for one trial (X-PLORE) the tildrakizumab NMA used 12 week data.
- For adalimumab all the trial primary endpoints are at 16 weeks but for two trials (CHAMPION and X-PLORE) the tildrakizumab NMA used 12 weeks instead. However, the data available from the publications of these studies shows there is only a very slight, if any, improvement in efficacy between the week 12 and 16 results.

4.3.2 Stage III NMA

As shown in Appendix table, all the trials available for the NMA had primary endpoints shorter than 28 weeks and for many of these trials the placebo control stopped at the primary endpoint. Therefore the ERG queried the nature of the data used in the Stage III NMA: were the data from a blinded, controlled phase of the study; an uncontrolled, blinded phase of the study; or an uncontrolled, unblinded phase of the study? In their clarification response the company provided this information (Table 63 of the clarification response) and stated,

"Although several studies dropped their placebo arms, there were often multiple intervention arms, so these are still considered to be active controls. We have noted where this is the case. The design of the later phases of the trials was often not reported in a great deal of detail so it is not always clear whether the remaining arms maintain their blinded status."

From Table 63 of the clarification response the ERG notes that of the 44 trials only 26 provided data at 24-28 weeks: 13 provided data at 24 weeks and 13 at 28 weeks. By drug:

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- Adalimumab – 7 trials' data, one not blinded and uncontrolled
- Apremilast -3 trials' data - 2 blinding unclear and uncontrolled
- Etanercept – 6 trials' data, 4 uncontrolled
- Guselkumab – 3 trials'data, all blinded controlled
- Ixekizumab – one trial's data – unblinded, uncontrolled
- Secukinumab – 4 trials' data – all blinded controlled
- Tildrakizumab – 2 trials' data – all blinded controlled
- Ustekinumab - 8 trials' data – one blinding unclear and uncontrolled.

The ERG notes that whilst much of the data used in this analysis is derived from blinded controlled comparisons, some are not. In particular, the data for apremilast, etanercept and ixekizumab is subject to a high risk of bias. Therefore this analysis will be less robust than that of the 12 -16 week time point. To check the reliability of the Stage III NMA the ERG asked the company to compare the results of this analysis with the results of direct comparison between individual treatments where such direct comparisons were available. The company provided this in their clarification response. This is discussed further in Section 4.4.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 NMA methods

The methods used for the NMA are detailed in CS Appendix D. The NMA focused on PASI response rates (PASI 50, 75, 90 and 100) because they have been considered to be the most relevant efficacy parameter in moderate to severe psoriasis, and the PASI response rate was the outcome that was consistently reported across all studies, and is the key efficacy parameter in the cost-effectiveness model. The ERG considers this appropriate but noted that the phase III trials' co-primary endpoints included the Physician's Global Assessment (PGA), which is considered to be an important outcome in clinical practice. The ERG asked the company to further justify why this outcome was not considered for a network meta-analysis. In their clarification the company explained further that the decision not to include PGA as a synthesised outcome measure was also influenced by the very high correlation between PGA and PASI which has been demonstrated (r^2 = 0.9157 for PASI 75 and PGA 0,1 at 8 to 16 weeks)[34] and the perspective expressed in the same publication that PASI is better validated and more detailed as a measure of efficacy.

The method used for modelling PASI responses followed the general principles outlined in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2:[35, 36] for each analysis the PASI response was modelled using a multinomial likelihood model with a probit link function. A summary of the model was provided in CS Appendix D9. Fixed- and random-effects approaches were explored.

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For the Stage I analysis (12-16 week data) the random-effects approach was reported to provide a better model fit to the observed data based on statistical goodness of fit statistics (DIC and total residual deviance). The results of this model, in terms of risk ratios relative to tildrakizumab 100 mg and tildrakizumab 200mg and to placebo are presented in CS Figures 20, 21 and 22 respectively.

Sensitivity analyses were undertaken, firstly including data from week 12 only; and secondly exploring the impact of placebo adjustment. The results of the 12 week data-only analysis were provided and showed little difference compared with the main analysis. ERG does not consider the first sensitivity analysis to be of particular importance; whether the 12 or 16 week data are used should reflect the appropriate time for assessment for a given treatment (as reflected in the main trials' primary endpoint). The company did not provide the results of nor details of the analysis with placebo adjustment: the CS stated only that, "The impact of placebo adjustment was assessed and found not to offer any advantages over the model without placebo adjustment". The ERG considers the issue of placebo adjustment to be of importance given the heterogeneity in the PASI response rates in the placebo arms of the included trials. The ERG requested full details of the results of the NMA using placebo adjustment for the Stage I analysis. These were provided in the company's clarification response –see Table 13.

Table 13 Measures of Stage I model fit, with/without placebo adjustment (Clarification response table 51)

	Fixed effect, no placebo adjustment	Fixed effect, placebo adjustment	Random effects, no placebo adjustment	Random effects, placebo adjustment
DIC	[redacted]	[redacted]	[redacted]	[redacted]
pD	[redacted]	[redacted]	[redacted]	[redacted]
Deviance = DIC - pD	[redacted]	[redacted]	[redacted]	[redacted]

DIC: deviance information criterion; pD: posterior mean of the deviance minus the deviance of the posterior means.

The model for placebo adjustment increases the uncertainty of estimating placebo effects, while decreasing the uncertainty for estimates for other treatment effects. This decrease, however, is not huge, and at the expense of an increase of effective variables (pD). As measured by DIC, the gain in deviance for placebo adjustments is not enough to justify the increase in effective variables.

In their clarification response the company provided additional sensitivity analyses requested by the ERG (including only Phase III trials; to include only licensed doses; and include infliximab). These were provided as both fixed and random effects models and adjusted for placebo or not.

For the Stage III NMA, in terms of model fit, the CS reported no substantial difference between FE and RE model (DIC = 1476.20 and pD = 55.82 for the FE model, DIC = 1478.53 and pD = 58.38 for the RE model). Both models provide similar mean values and 95% credibility intervals for risk ratios.

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There was some heterogeneity in Placebo treatment responses, particularly at PASI 50 (I^2 = 74% at PASI 50, I^2 = 28% at PASI 75, I^2 = 0% at PASI 90 and 100). And therefore the CS stated a preference the RE model, keeping the model choice consistent with the Stage I model.

4.4.2 NMA Results

Stage I NMA

The results for the Stage I NMA (RE, not placebo adjusted) relative to placebo are presented in [redacted] The ERG notes that these results are similar to those from the ICER NMA (that included only phase III trials) except that in the ICER results adalimumab was more efficacious with less overlap with tildrakizumab.

The results of the additional sensitivity analyses requested by the ERG (provided by the company in their clarification response) showed little difference from the main analysis. For the reasons discussed earlier the ERG considers that the most appropriate analysis is that including infliximab; the model fit statistics (Table 60 of clarification response) indicate that the RE non-placebo adjusted model is the best fit.

The results for infliximab relative to placebo are presented in [redacted] The results for apremilast and DMF (also taken from the infliximab NMA) are also included in this table. Note that these results are presented for each treatment versus placebo (larger effect size indicates better treatment), unlike in [redacted] where the results are presented for placebo versus treatment (smaller effect size indicates better treatment).

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Table 14 Redacted

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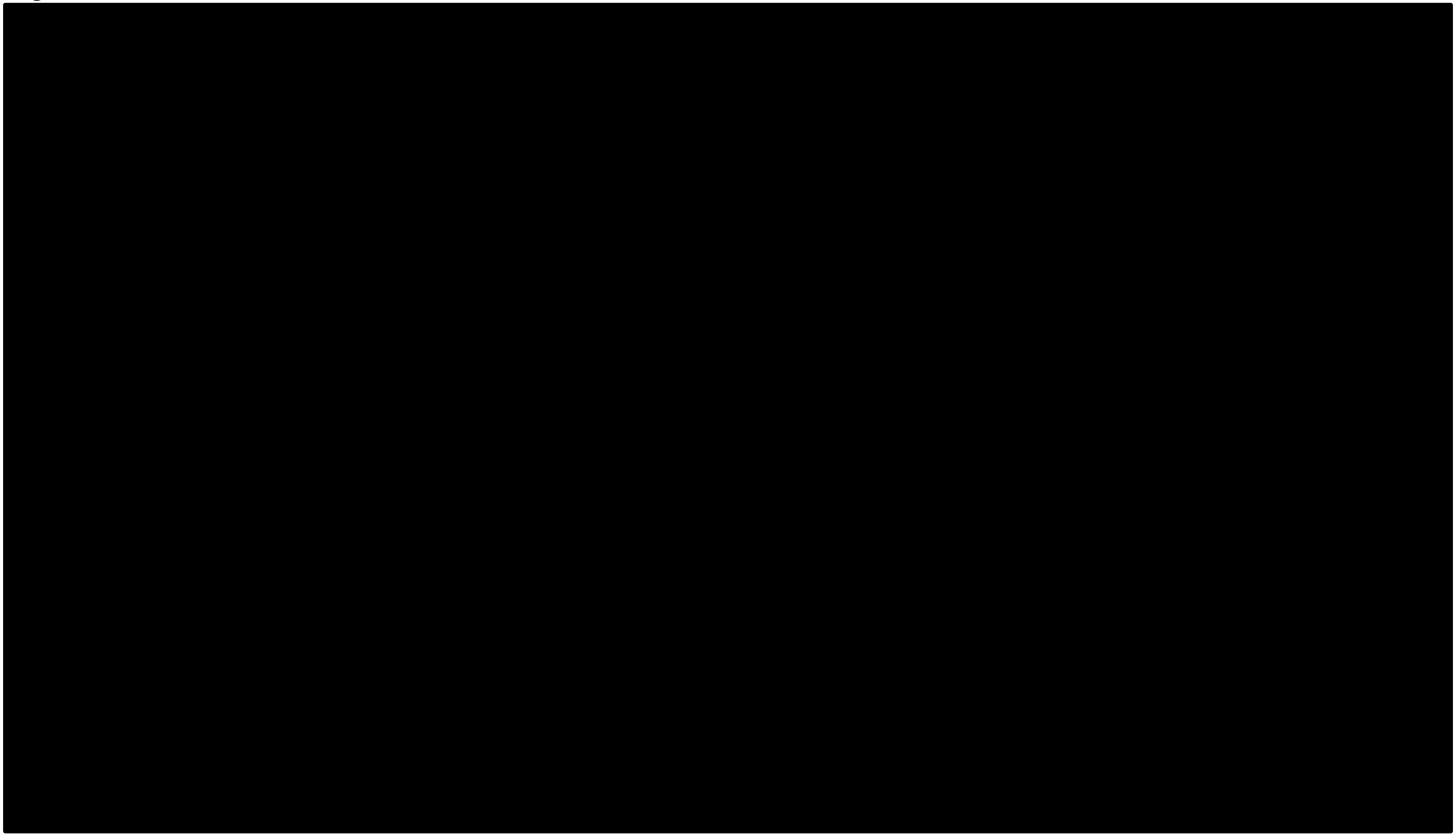
Figure 8 Redacted



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Stage III NMA

The results of the Stage III NMA reveal a similar pattern of relative efficacy across tildrakizumab and its comparators as the Stage I analysis did, i.e. that for all levels of PASI response tildrakizumab 100 mg and 200mg is more efficacious than etanercept and is less efficacious than brodalumab, guselkumab, secukinumab and ixekizumab. In the Stage III analysis adalimumab appears slightly less efficacious than tildrakizumab, whilst ustekinumab appears slightly more so. The results are summarised in Table 16

A simple comparison of the relative risks against placebo across the two analyses reveals that for all levels of PASI response tildrakizumab 100 mg and 200mg is more efficacious at week24/28 (see Table 15). However, this pattern is repeated for all the comparators with at least one PASI outcome and so it is unclear whether the improved efficacy at the later time point is a particular feature of tildrakizumab common across biologics in moderate to severe plaque psoriasis. Bearing in mind that the Stage III NMA is less robust and may be less reliable than the Stage I analysis, firm conclusions cannot be draw from this.

To check the reliability of the Stage III NMA the ERG asked the company to compare the results of this analysis with the results of direct comparison between individual treatments where such direct comparisons were available. The company provided this in Tables 99 and 100 of their clarification response. The risk ratios from the random effects model are presented in Table 16.

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Table 15 Comparison of results from Stage I (12/16 week) and Stage III (24/28 weeks) networks (RE, no placebo adj, not including infliximab)

Values >1 favour treatment in top row	Tildrakizumab 100mg Wk 0, 4	Tildrakizumab 200mg Wk 0, 4	Adalimumab 40mg Q2Wld	Brodalumab 210mg Q2W	Etanercept 50mg QW	Guselkumab 100mg Q8W	Ixekizumab 80mg Q4W	Secukinumab 300mg Q4W	Ustekinumab 45mg Wk 0, 4, Q12W	Ustekinumab 45_90mg Wk 0, 4, Q12W, 16, (28)	Ustekinumab 90mg Wk 0, 4, Q12W
PASI 50 Vs Placebo 12/16 week data (RE, npa)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50 Vs Placebo 24/28 week data (RE, npa)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75 Vs Placebo 12/16 week data (RE, npa)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75 Vs Placebo 24/28 week data (RE, npa)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90 Vs Placebo 12/16 week data (RE, npa)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90 Vs Placebo 24/28 week data (RE, npa)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Values >1 favour treatment in top row	Tildrakizumab 100mg Wk 0, 4	Tildrakizumab 200mg Wk 0, 4	Adalimumab 40mg Q2Wld	Brodalumab 210mg Q2W	Etanercept 50mg QW	Guselkumab 100mg Q8W	Ixekizumab 80mg Q4W	Secukinumab 300mg Q4W	Ustekinumab 45mg Wk 0, 4, Q12W	Ustekinumab 45_90mg Wk 0, 4, Q12W, 16, (28)	Ustekinumab 90mg Wk 0, 4, Q12W
PASI100 Vs Placebo 12/16 week data (RE, npa)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI100 Vs Placebo 24/28 week data (RE, npa)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table 16 Comparison of direct and indirect evidence for the Stage III analysis: risk ratios from the random effects model (adapted from Table 100 of Clarification response)

RANDOM EFFECTS MODEL				Risk Ratio	
PASI	T1	T2	p_{sym}	direct	indirect
PASI 50	Placebo	Adalimumab 40mg Q2Wld	[redacted]	[redacted]	[redacted]
PASI 75	Placebo	Adalimumab 40mg Q2Wld	[redacted]	[redacted]	[redacted]
PASI 90	Placebo	Adalimumab 40mg Q2Wld	[redacted]	[redacted]	[redacted]
PASI 100	Placebo	Adalimumab 40mg Q2Wld	[redacted]	[redacted]	[redacted]
PASI 75	Placebo	Guselkumab 100mg Q8W	[redacted]	[redacted]	[redacted]
PASI 90	Placebo	Guselkumab 100mg Q8W	[redacted]	[redacted]	[redacted]
PASI 100	Placebo	Guselkumab 100mg Q8W	[redacted]	[redacted]	[redacted]
PASI 75	Placebo	Secukinumab 300mg Q4W	[redacted]	[redacted]	[redacted]
PASI 90	Placebo	Secukinumab 300mg Q4W	[redacted]	[redacted]	[redacted]
PASI 100	Placebo	Secukinumab 300mg Q4W	[redacted]	[redacted]	[redacted]
PASI 75	Placebo	Ustekinumab 45_90mg*	[redacted]	[redacted]	[redacted]
PASI 90	Placebo	Ustekinumab 45_90mg*	[redacted]	[redacted]	[redacted]
PASI 100	Placebo	Ustekinumab 45_90mg*	[redacted]	[redacted]	[redacted]
PASI 50	Tildrakizumab 100mg Wk 0, 4	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 75	Tildrakizumab 100mg Wk 0, 4	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 90	Tildrakizumab 100mg Wk 0, 4	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 100	Tildrakizumab 100mg Wk 0, 4	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 50	Tildrakizumab 200mg Wk 0, 4	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 75	Tildrakizumab 200mg Wk 0, 4	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]

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PASI 90	Tildrakizumab 200mg Wk 0, 4	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 100	Tildrakizumab 200mg Wk 0, 4	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 50	Etanercept 50mg QW	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 100	Secukinumab 300mg Q4W	Ustekinumab 45_90mg*	[redacted]	[redacted]	[redacted]
PASI 75	Secukinumab 300mg Q4W	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 90	Secukinumab 300mg Q4W	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 100	Secukinumab 300mg Q4W	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 75	Secukinumab 150mg Q4W	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 90	Secukinumab 150mg Q4W	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]
PASI 100	Secukinumab 150mg Q4W	Etanercept 50mg BIW_rd	[redacted]	[redacted]	[redacted]

* Wk 0, 4, Q12W, 16, (28)

The indirect risk ratio as calculated by the indirect evidence network is compared with the direct risk ratio as calculated by the direct evidence network. The p_{sym} is the measure of how close the calculated risk ratios are from both direct and indirect evidence, taking into account variation: a value smaller than 0.05 indicates a fairly large distance. From Table 16, using the cut off of psym 0.05, only the ustekinumab vs placebo results are inconsistent, with the indirect results underestimating the treatment effect. However, Table 16 reveals that the results of placebo comparisons from the indirect analysis for all other treatments were generally to a greater or lesser extent, inconsistent with those from the direct comparisons, though whether the treatment effect was over – or underestimated varied across treatment, and for adalimumab and guselkumab they also varied across outcomes; for secukinumab the indirect results overestimated the direct treatment effects. For the comparisons between active treatments, which were mostly based on single direct comparison trials, the results of the indirect analysis were consistent with the direct comparison. The ERG notes that whilst not reflected in low psym values, the PASI 100 results are underestimated by the indirect analysis; this impacts mostly on etanercept.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable.

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4.6 Conclusions of the clinical effectiveness section

The clinical efficacy data on tildrakizumab came from three well-conducted randomised control trials: one phase IIb dose finding trial; and two phase III trials, reSURFACE1 and reSURFACE2. All three trials had a placebo controlled phase – 12 weeks for the two reSURFACE trials and 16 weeks for the Phase IIb trial. reSURFACE2 also included a randomised comparison with etanercept up to 28 weeks.

In reSURFACE1 and reSURFACE2 for the co-primary outcomes, the proportion of PASI 75 and clear or minimal PGA responders, and key secondary endpoints PASI 90 and PASI 100, tildrakizumab 100mg and 200mg performed statistically significantly better than placebo at 12 weeks. Also, when compared with placebo, tildrakizumab was associated with statistically significant improvements in health-related quality of life, as assessed by the Dermatology Quality of life index (DLQI). In reSURFACE2, compared with etanercept, tildrakizumab 100mg and 200mg performed statistically significantly better for all outcomes at 12 weeks and 28 weeks except for clear or minimal PGA at 12 weeks.

There is a question over how appropriate the primary endpoint assessment time was, being 12 weeks in the Phase III trials, given that response rates are higher at later time points and in the anticipated licence (smPC), assessment is recommended at week 28.

The proportion of patients within reSURFACE1 and reSURFACE2, previously treated with biologic therapy before commencing treatment with tildrakizumab was low – around 20% across the two trials, whereas in clinical practice it is unlikely that tildrakizumab would be used first line after non-biologic treatment. In addition the proportion of patients previously treated with a systematic non-biologic therapy at baseline across both trials (total across arms in reSURFACE1 and reSURFACE2, [redacted] respectively) is likely to be lower than would be seen in clinical practice, where the vast majority of patients are expected to receive systematic non-biologic therapy prior to commencing biologic treatment options.

The pre-specified subgroup analyses of week 12 data found no clinically relevant effect of previous use of a biologic and there was no effect of baseline weight ≤90kg and >90kg - for PASI 75 and PGA ‘clear’ or ‘minimal’ responses. However, there is a suggestion of a higher response rate in patients weighing < 90kg than in heavier patients for the 100 mg dose and 200mg dose for PASI 90. Patients with a baseline PASI < 20 also responded slightly better than those with higher PASI; this effect was most obvious for PGA 0/1. Without formal tests for interactions, it is difficult to draw firm conclusions and the trials were not powered to detect difference between dose regimens. At 12 weeks there was no apparent effect of phototherapy/systemic non-biological therapy.

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Based on data presented at 28 weeks, the ERG does not find the evidence of a better response with the 200 mg dose in patients weighing >90kg, as reported in the CS, convincing, noting that similar differences between the doses was seen in patients ≤90kg. For patients with a baseline PASI ≥20 the evidence for a better response with the 200mg dose (at week 28) is a little stronger.

Longer term data

The results presented in the CS for the longer-term phases of the reSURFACE trials are of limited value in terms of providing robust clinical effectiveness data. This is due to a lack of control groups; a lack of blinding, the use of 'as observed' datasets, which exclude many of the non-responders and drop-outs; and some decisions made regarding the continuation or discontinuation of tildrakizumab which were not reflective of those which would be made in NHS practice.

Adverse events

Tildrakizumab appears to have an acceptable safety profile with the incidence of treatment emergent adverse events (TEAEs), serious TEAEs, discontinuations due to AEs, and severe infections being comparable across all four trial interventions used in the two reSURFACE trials.

NMA

The NMA presented in the CS compared the efficacy of tildrakizumab (100 mg and 200 mg) with the therapies adalimumab, apremilast, brodalumab etanercept, ixekizumab, risankizumab, guselkumab, secukinumab, ustekinumab and DMF. The company also submitted a NMA including infliximab. Appropriate methods were used to identify the trials for this analysis, although these were not used to identify the infliximab trials. Comparing the trials included with those included in other comparable recent NMAs indicates that the included trials are appropriate.

The methods used for the NMA appear appropriate although it is possible that the efficacy of adalimumab was slightly underestimated due to the selection of 12 week rather than 16 week data for a small number of trials. The Stage III (24/28 weeks) NMA is less robust and may be less reliable than the Stage I (12/16 weeks) NMA as it includes extrapolated placebo data and some uncontrolled treatment data, so firm conclusions cannot be drawn from this.

The results for the company's base case Stage I NMA (assessment at 12-16 weeks) (RE, not placebo adjusted) relative to placebo found that for all levels of PASI response tildrakizumab 100 mg and 200mg is more efficacious than etanercept and similar to adalimumab and ustekinumab. It is less efficacious than brodalumab, guselkumab, secukinumab and ixekizumab. The ERG notes that these results are similar to those from the ICER NMA (that included only phase III trials) except that in the ICER results adalimumab was more efficacious with less overlap with tildrakizumab. The results of

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the additional sensitivity analyses requested by the ERG (provided by the company in their clarification response) showed little difference from the main analysis. This included the analysis including infliximab (RE non-placebo adjusted model) which the ERG considers the most appropriate analysis. From this analysis additional results found tildrakizumab to be less efficacious than infliximab but more efficacious than both apremilast and DMF.

The results of the Stage III (24-28 weeks) NMA reveal a similar pattern of relative efficacy across tildrakizumab and its comparators as that from the Stage I analysis. A simple comparison of the relative risks against placebo across the Stage I and Stage III analyses reveals that for all levels of PASI response tildrakizumab 100 mg and 200mg and all the comparators are more efficacious at week 24/28. Therefore, it is unclear whether the improved efficacy at the later time point is a particular feature of tildrakizumab or is common across biologics in moderate to severe plaque psoriasis.

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5 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided in response to the points for clarification. The submission was subject to a critical review on the basis of the company's report and by direct examination of the economic model.

The economic submission included:

1. A systematic literature review (SLR) to identify prior evidence on the cost-effectiveness of tildrakizumab for moderate to severe plaque psoriasis and to support the development of the cost-effectiveness model (summarised in CS section B.3.1 with full details presented in Appendix G).

2. Two additional SLRs to identify relevant health-related quality of life (HRQoL) data (Appendix H) and resource use/cost data (Appendix I).

3. A description of the economic model including inputs and assumptions (Sections B.3.2-B.3.11) .

4. An electronic version of economic model developed in Microsoft Excel ®.

In response to points for clarification, the company further submitted:

5. A series of additional NMA analyses, updated EQ-5D data and a revised economic model.

The ERG notes that the CS does not include the confidential PAS schemes which have been approved for brodalumab, guselkumab, ixekizumab and secukinumab.

5.1 ERG comment on company's review of cost-effectiveness evidence

A SLR was undertaken by the company to identify previously published cost-effectiveness studies of tildrakizumab for moderate to severe plaque psoriasis. Full details of the search strategies are presented in Appendix G of the CS.

5.1.1 Searches

Searches of the following electronic databases were undertaken: Medline®, Medline® In-Process (and other non-indexed citations), Embase, EconLit, Cochrance Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), NHS Economic Evaluation Database (NHS EED), Cost-Effectiveness Analysis (CEA) Registry, Clinical Trials.gov, WHO International Cliniical Trials Registry Platform (WHO ICTRP) and EconLit. The searches also included 12

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conference websites (last 3 years) and 2 organisations (EMA, FDA). The ERG considers that the databases used for the cost effectiveness review are suitable to ensure that all potentially relevant records are identified.

Additional searches of conference websites were carried out to identify potentially relevant posters and abstracts and the reference lists of identified studies were reviewed.

The search strategies used in each of the databases are fully reproduced in Figure 25 (pages 230 to 237) with the date of the search being given as well as the numbers of records retrieved from each of databases. The methods used to search and scan conference websites is also described in detail. The search strategy used in all of the database searches consists simply of the term "tildrakizumab" and synonyms. This is entirely appropriate as all the numbers retrieved are relatively small so there is no need to make use of a search filter within the strategy.

The ERG considers that thorough searches of appropriate databases and conference proceedings were undertaken.

5.1.2 Inclusion/exclusion criteria used for study selection

Only economic evaluations (cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses, cost-minimisation analyses) of tildrakizumab compared to any comparator were included.

The ERG considers that the company used appropriate inclusion/exclusion criteria for study selection.

5.1.3 Studies included and excluded in the cost effectiveness review

After deduplication, 194 records were assessed for relevance. Two reviewers independently assessed the titles and abstracts of these records, using the information in the titles and abstracts. No relevant studies were identified.

The ERG considers that the company used appropriate approaches to identify relevant studies.

5.1.4 Conclusions of the cost effectiveness review

No previous studies examining the cost-effectiveness of tildrakizumab were identified. As a result, the company developed a *de novo* cost-effectiveness model for the purposes of this appraisal.

The ERG considers that the company's conclusions are appropriate and the de novo cost-effectiveness model is the only relevant source of evidence concerning the cost-effectiveness of tildrakizumab for moderate to severe plaque psoriasis.

5.2 ERG's summary and critique of company's submitted economic evaluation

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An overview of the company's economic evaluation is presented in Table 17 and a quality checklist is presented in a separate appendix (Table 1; Addendum I quality checklist)

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Table 17 Summary of the company's economic evaluation

Element of HTA	Approach	Source/Justification	Location in CS
Model Structure	A treatment sequence Markov model was developed for the cost-effectiveness analysis. The model consists of four treatment-related health states (induction, maintenance, best supportive care and death) with patients being allocated to one of four PASI response categories (PASI <50, PASI 50-74, PASI 75-89, PASI ≥90).	Consistency with previous NICE appraisals. Enables treatment sequences to be evaluated over an appropriate time horizon. Captures treatment specific effects on PASI response.	Section B.3.2 (p.90-92), Table 25 (p. 93)
Population	Population currently eligible for biologic treatment for psoriasis in the NHS, i.e. patients with severe psoriasis, defined as a PASI score ≥10 and a DLQI>10, who have failed to respond to, or are unable to be treated with conventional systemic therapies.	Aligned with population considered in previous NICE appraisals for biologic therapies (TA103, TA146 TA350, TA442, TA511 and TA521)	Section B.3.2 (p. 90)
Intervention and comparators	Different treatment sequences were considered, consisting of three lines of biologic treatments followed by BSC: Tildrakizumab-Ustekinumab-Secukinumab-BSC Adalimumab-Ustekinumab-Secukinumab-BSC Ustekinumab – Adalimumab-Secukinumab-BSC Secukinumab – Ustekinumab – Adalimumab – BSC Etanercept – Ustekinumab – Secukinumab – BSC Ixekizumab – Ustekinumab – Secukinumab – BSC Brodalumab – Ustekinumab – Secukinumab – BSC Guselkumab – Ustekinumab – Adalimumab – BSC	The comparators included biologic treatments recommended by NICE for the treatment of psoriasis after systemic non-biologic therapy has failed or was not tolerated. Four comparators included in the NICE scope (apremilast, dimethyl fumarate, infliximab and BSC) were not considered by the company to be relevant comparators and were excluded. BSC was included but only as the final treatment option in all sequences. The length of the sequences was based on clinical expert advice. The positioning of biologics in the sequence was informed by BAD guidelines and clinical expert advice. [37] The sequences were further justified as providing a focused analysis based on the most clinically plausible sequences and also ensuring that each comparator was included in at least one sequences as a frontline treatment.	Sections B.3.2 (p. 95-98) and Table 27 (p.97)
Perspective, time horizon and discounting	NHS and PSS perspective. A lifetime time horizon (approx. 58 years) was employed and a discount rate of 3.5% was applied to both costs and QALYs	The perspective and discounting were consistent with the NICE reference case.	Section B.3.2 (p.91-92), Table 25 (p. 93)

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		A lifetime horizon was considered necessary to fully capture the incremental costs and benefits associated with the treatment sequence.	
Treatment effectiveness and extrapolation	Results from the NMA were used to inform the probability of response to treatment, by PASI category (<50, 50-74, 75-89, ≥90), during the induction period of each treatment. The effectiveness of treatments was assumed to be independent of the position within a given sequence. Treatment continuation to the maintenance phase was dependent on PASI ≥75 response at the end of the induction period. Treatment discontinuation during the maintenance phase was fixed at a constant annual rate of 18.7% for all treatments. This incorporates withdrawal due to loss of response and adverse events. Choice of treatment assumed to have no impact on mortality rate.	Results from the NMA ensure all available evidence on the response to treatments is considered, addressing the lack of head-to-head trials. Aligned with previous NICE appraisals. Variable evidence from the literature and not considered to be a significant cost-effectiveness driver. Aligned with previous NICE appraisals. Consistency with the assumptions and discontinuation rate used in TA511. Derived from a UK-based registry (BADBIR).[8] Aligned with previous NICE appraisals and clinical advice.	Section B.3.3. (p. 98-103)
Health-related quality of life (HRQoL)	Estimates based on EQ-5D-3L data collected in the reSURFACE 1 trial at week 12. Based on patient level data from the subgroup with DLQI>10 only (n=482). [5] Utility values were based on the European valuation set. Utility values were assumed to be dependent only on the health state (by PASI response). An adjustment was included to account for ageing.	Aligned with previous submissions and consistent with the NICE reference case. Not justified in submission. Aligned with previous submissions. To account for impact of ageing given the long time horizon.	Section B.3.4 (page 103-106), Table 33 (p.106)
Resources and Costs	Costs and healthcare resource use considered included: Drug Acquisition Administration Monitoring BSC	Drug acquisition costs for tildrakizumab (induction and maintenance periods) based on the Patient Access Scheme (PAS). Costs for comparators based on list prices given confidential nature of discounts. Biosimilar costs assumed for etanercept. No additional costs assumed for administration. All treatments given by self-administered SC injection and	Section B.3.5, Table 35 (p. 108). Table 36 (p. 111), Table 37 (p. 111)

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		choice of treatment assumed to have no impact on administration costs. Monitoring costs based on NICE clinical guidelines (CG153). BSC costs based on estimates from NICE clinical guideline (CG153).	
Adverse events	No included.	Rate of adverse events considered to be low for tildrakizumab. Inclusion not expected to have any meaningful impact.	Section B.3.4 (p. 106)
Subgroups	No clinically defined subgroup analysis is reported in the CS.	Not justified in submission. Scenario analyses used to explore 3 different assumptions concerning the proportion of patients receiving 200mg dose of tildrakizumab: (i) body weight ≥90kg, (ii) baseline PASI ≥20 (iii) body weight ≥90kg, & baseline PASI ≥20.	Section B.3.8.4 (p.131-139), Tables 46-48 (p. 138-139)
Sensitivity analysis	The company performed both one-way and probabilistic sensitivity analysis. A series of scenarios using alternative assumptions were also presented	Justified based on the NICE reference case and the current methods guide.	Section B.3.8 (p. 119-)

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5.2.1 NICE reference case checklist

The NICE reference case checklist is given in Table 18.

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Table 18: NICE reference case checklist

Element of economic evaluation	**NICE Reference Case**	**Included in submission**	**Comment on whether *de novo* evaluation meets requirements of NICE reference case**
Defining the decision problem	As per NICE scope	Partially	The NICE scope refers to "*adults with moderate-to-severe plaque psoriasis"*, i.e. all patients covered under the licensed indication which includes conventional systemic treatments. The population in the company submission is more restrictive and focuses on adults for whom standard systemic therapies have failed or are not tolerated/contraindicated. Therefore, the company positions tildrakizumab together with other systemic biologic therapies, anticipating it will be used at a similar point to the current NICE pathway for biologic therapies.
Comparator(s)	As listed in the scope developed by NICE	Partially	The company states that the most appropriate comparators are other biologic therapies. A total of seven comparators identified in the NICE scope were included in the analysis: ustekinumab, secukinumab, adalimumab, etanercept, ixekizumab, brodalumab and guselkumab. Four comparators included in the NICE scope (apremilast, dimethyl fumarate, infliximab and BSC) were not considered to be relevant comparators and were excluded. Apremilast and dimethyl fumarate were argued to be positioned in a different part of the NICE psoriasis treatment pathway and were considered to be used either prior to biologic treatments or in patients unsuitable for biologic treatments. Infliximab was not considered a relevant comparator as this is only approved by NICE for patients with very severe psoriasis (PASI≥20 and DLQI>18). BSC was not considered a relevant comparator as it contains no active therapy. However, BSC was included as the final option within each sequence. A restricted set of 'all feasible' sequences were compared. Tildrakizumab was only evaluated as a first line treatment option within these sequences.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes	
Perspective on cost	NHS and PSS	Yes	

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Element of economic evaluation	**NICE Reference Case**	**Included in submission**	**Comment on whether *de novo* evaluation meets requirements of NICE reference case**
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes	
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	Yes	The base case includes a lifetime time horizon (approx. 58 years), which is considered sufficiently long to account for all important differences between the comparator sequences.
Synthesis of evidence on health effect	Based on systematic review	Partially (Yes in response)	A systematic review was undertaken to collect all available evidence on relevant health effects from published studies and previous submissions. However, it is unclear why: (i) some treatments that were not considered to be relevant comparators were included in the NMA to strengthen the overall network (e.g. apremilast and dimethyl fumarate) and others were excluded (e.g. infliximab); (ii) some unlicensed treatments not included in the scope were included in the NMA (e.g. risankinzumab) and others were excluded (e.g. certolizumab pegol). The company's response to clarification included a revised NMA including infliximab trials.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes	
Source of data for measurement of health-related quality of life	Reported directly by patients or carers	Yes	EQ-5D-3L collected alongside the reSURFACE 1 trial. [5]
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No (Yes in company response)	Utilities were reported in the CS to have been calculated using the European valuation set for EQ-5D-3L The European valuation set is based on survey data from six Western European countries (Finland, Germany, The Netherlands, Spain, Sweden and the UK) using EQ-5D visual analogue scale (VAS) scores.

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Element of economic evaluation	**NICE Reference Case**	**Included in submission**	**Comment on whether *de novo* evaluation meets requirements of NICE reference case**
			The company's response to clarification confirmed that the source of preference data had been incorrectly reported in the CS. The company clarified that the appropriate UK value set was in fact used on all non-USA based patients, whilst the USA value was used on USA patients within the dataset. The company also provided a re-analysis of the dataset applying the UK value set to all patients
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	All QALYs are given the same weight
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes	

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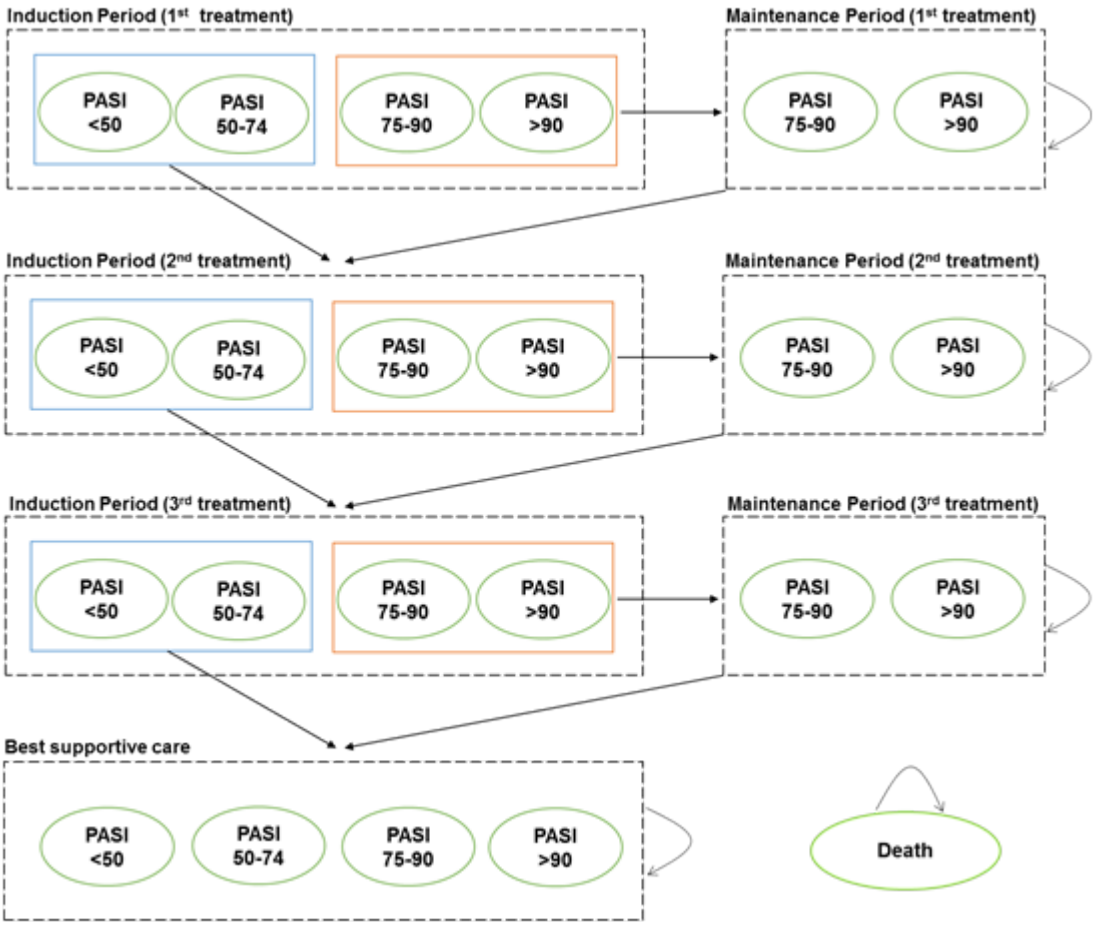
5.2.2 Model structure

The economic evaluation of tildrakizumab was undertaken using a Markov state-transition model developed in Microsoft Excel ®. The use of a Markov approach was justified based on the need to model treatment sequences over an appropriate time horizon. The structure of the model is showed in Figure 9.

Figure 9 Schematic representation of treatment sequence Markov model (CS figure 23 p.92)



The model consists of four main treatment-related health states (induction, maintenance, best supportive care and death) with patients being allocated to one of four PASI response categories (PASI <50, PASI 50-74, PASI 75-89, PASI ≥90). The model structure allows for alternative sequences including three lines of biologic treatment followed by BSC.

Each line of treatment in a sequence starts with an induction period lasting 14 weeks. At the end of the induction period, individuals are assigned to one of the four PASI response categories based on the NMA results. Individuals who achieve a response of PASI≥75 are assumed to continue with the same treatment and enter the maintenance phase of the model. Individuals who achieve PASI<75 are assumed to discontinue their treatment and then switch to the next treatment in the sequence starting

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with the induction period. The utility values during the induction period are based on the PASI response categories (PASI <50, PASI 50-74, PASI 75-89, PASI ≥90) assessed at the end of the induction period, i.e. patients immediately achieve the HRQoL associated with their PASI response.

During the maintenance period, individuals are assumed to continue to receive the same treatment and maintain the same PASI response until discontinuation, due to loss of response and/or adverse events. In line with previous NICE TAs, the company base-case assumes that individuals discontinue treatment at a constant annual rate.

Individuals who do not respond to the third line of treatment (or who initially respond but then subsequently discontinue treatment) enter the BSC state. The BSC state is not formally defined in the submission, although the resource costs estimates imply a combination of non-biologic drug therapy, phototherapy, day centre care and inpatient care. Upon entry to the BSC state, patients are distribued to PASI response categories and associated HRQoL according to the placebo PASI response rates estimated using the NMA. Patients remain in this state until the end of the model time horizon or death. Mortality is not conditioned on treatment or PASI response and is derived from UK lifetables.

Adverse events were not included in the model. The company noted that biologic therapies are well tolerated in this indication with a low adverse event rate and the exclusion of these events was not expected to alter the results of the analysis.

A 14-week cycle length was adopted to account for the different induction period for the different treatments (between 12 to 16 weeks) and a half-cycle correction was applied. The 14 week cycle was chosen to represent the midpoint of the range of induction periods across the different treatments and to help simplify the model structure.

ERG commentary

The model structure is generally consistent with the most recent NICE TA appraisals which have assessed treatment sequences. However, the ERG notes that several recent submissions (e.g. TA442, TA511) have separated the PASI≥90 state into two states: PASI 90-99 and PASI 100 (complete clearance). The ERG requested further justification from the company for why a single state for PASI ≥90 state was used. The company responded that a larger number of previous appraisals did not include a separate state for PASI 100 and hence they chose to adopt the most common model structure. The company also stated that the addition of a separate PASI 100 state would not result in any meaningful impact, given the small difference in HRQoL reported between the PASI 90-99 and PASI 100 states in TA 442 and TA511. The ERG was satisfied with the company's additional justifications.

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The model base case assumes that the clinical assessment of response for tildrakizumab will occur at 12 weeks. However, as the model uses 14 week cycles, the base case assumes that this assessment will happen 14 weeks after treatment with tildrakizumab is initiated. The ERG also notes that company argues in other parts of their submission that the appropriate time point to assess treatment response for tildrakizumab should be at 28 weeks; stating that "*it would be biologically implausible, evidentially premature, and clinically burdensome to specialists and patients, to implement an assessment and stopping rule at week 12*".

The ERG sought further justification for why the company assumed a 14 week stopping rule for tildrakizumab in their base case analysis. The company responded that the 14 week time point was chosen because the choice of stopping rule for the comparator treatments (between 12 to 16 weeks) has conventionally been based on the time point at which the primary outcome measure was assessed within the pivotal studies. The company concluded that it was preferable to use analyses more closely aligned with the time point of the primary analysis for tildrakizumab. The company also highlighted that this may lead to conservative outcomes for tildrakizumab, citing more favourable cost-effectiveness results from a scenario analysis using a 28 week stopping rule for tildrakizumab.

A 12-week response assessment period for tildrakizumab would be consistent with the time point of the primary outcome in the reSURFACE studies. [5] However, the draft Summary of Product Characteristics (SmPC) also states that: "*Consideration should be given to discontinuing treatment in patients who have shown no response after 28 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 28 weeks.*".

The ERG highlights the uncertainty surrounding the most clinically appropriate response assessment period for tildrakizumab and also the cost-effectiveness of alternative stopping rules (also see 4.2.6). The ERG notes that the company reported a separate scenario analysis which they concluded demonstrated more favourable cost-effectiveness results for tildrakizumab using a 28 week stopping rule. As discussed below, the ERG considers that these conclusions may be potentially misleading due to the inappropriate assumptions made for the comparator regimens (i.e. that they would also have a 28 week stopping rule). The ERG also believes that the cost-effectiveness of alternative stopping rules for tildrakizumab would be most appropriately informed by treating these as separate comparators. In this manner, the incremental effectiveness and cost-effectiveness of alternative response periods could be more formally assessed.

The decision to use a cycle length of 14 weeks results in a mismatch between the time point of the primary outcomes reported in the reSURFACE trials (12 weeks) and the time point of the response assessment assumed in the cost-effectiveness model (14 weeks). [5] The company justified the choice of

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cycle length in order to simplify the model structure. The company reported that a 14 week time point represents the midpoint of induction periods for the other comparator treatments (12 or 16 weeks). The ERG sought further clarification from the company for this assumption during the clarification stage, noting in their clarification question that shorter cycle lengths (e.g. 2 weeks) would have ensured that the stopping rules for tildrakizumab and for the comparator treatments could have been precisely matched to the proposed timing of the stopping rule for tildrakizumab and the NICE approved stopping rules for the comparator treatments (see Table 19).

Table 19: Summary of response assessment periods reported in previous NICE appraisals

Drug	Duration	Source
Adalimumab	16 weeks	NICE TA 455[3838]
Apremilast	16 weeks	NICE TA 368
Brodalumab	12 weeks	NICE TA 511
Dimethyl fumarate	16 weeks	NICE TA 475
Etanercept	12 weeks	NICE TA 103
Guselkumab	16 weeks	NICE TA 521
Infliximab	10 weeks	NICE TA 134
Ixekizumab	12 weeks	NICE TA 442
Secukinumab	12 weeks	NICE TA 350
Ustekinumab	16 weeks	NICE TA 180

The company response stated that the use of two-week cycles would substantially increase the size and complexity of the model and increasing the risk of programming errors. The company also stated that efficacy and costs were fully captured in the economic model with a 14-week cycle length.

The ERG disagrees with the company's rationale and has significant concerns regarding the biases that may arise from using a common stopping rule for all treatments. While the ERG acknowledges that using shorter cycles would increase the size and complexity of the model, the risk of introducing additional errors needs to be weighed up against possible biases created when assuming a common 14 week stopping rule. In particular, the ERG highlights that the company's approach creates an important source of bias in relation to the costs of the induction period for treatments with shorter or longer recommended response assessment periods. The significance and potential magnitude of this

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bias depends on the frequency of administration of particular treatments during the induction periods. This issue is further discussed in the resource use and cost section of the ERG report.

In conclusion, while the model structure is generally consistent with the most recent NICE TA appraisals, the company's model should have used shorter cycle lengths to more accurately represent the different induction periods and avoid introducing potential biases arising from the use of a common assessment period.

5.2.3 Population

Tildrakizumab is indicated "for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy" (CS, p.10). However, the CS proposed a more restrictive positioning for tildrakizumab aligned with the positioning of other biologic therapies recommended by NICE. Consistent with this positioning, the population considered were adults with moderate to severe plaque psoriasis who are eligible for biologic treatment in the NHS (i.e., having a PASI score ≥10 and a DLQI>10) and who have failed to respond to, or are unable to be treated with conventional systemic therapies. Patients entering the model were assumed to be aged 46 years and exactly half (50%) of cohort were assumed to be male.

ERG commentary

Although the population considered in the CS is more restrictive than the product licence and the NICE scope, the ERG considers that this restriction is appropriate in the context of an STA appraisal and is consistent with the population considered in previous NICE TAs for other biologic treatments.

The starting age of the model (46 years) was based on the mean age in the reSURFACE 1 and 2 studies. [5] The gender distribution assumed (50:50 male to female ratio) was based on a UK epidemiological study reporting on the prevalence and treatment of psoriasis. The ERG highlights that a much higher proportion of the patients within each of the arms of the reSURFACE 1 and 2 trials were male (65%-73% across the separate trial arms). [5] The higher proportion of males in these trials also appears consistent with the findings from European Registries for systemic psoriasis treatment which report a similar dominance of registered men. The recent study by Hagg et al (2017), found that women have less severe psoriasis compared with men, after controlling for possible confounders.[39]

The ERG concludes that the company model should have informed the gender distribution using the reSURFACE trial characteristics or from epidemiological studies of people with moderate to severe psoriasis. [5] However, the ERG does not consider that the company's approach creates any meaningful bias given that the treatments are not assumed to have any effect on the mortality rate itself.

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5.2.4 Interventions and comparators

Table 20 summarises the treatment sequences compared in the company base-case. A total of 8 treatment sequences were evaluated. These sequences include three lines of biologic therapy followed by BSC. Tildrakizumab is included in a first line position alongside other comparators recommended by NICE for psoriasis patients who have failed to respond to conventional systemic therapies or who are intolerant or have a contraindication to these treatments.

Table 20: Treatment sequences compared in the company base-case

Sequence	1st line	2nd line	3rd line	4th line
1	Tildrakizumab	Ustekinumab	Secukinumab	BSC
2	Adalimumab	Ustekinumab	Secukinumab	BSC
3	Ustekinumab	Adalimumab	Secukinumab	BSC
4	Secukinumab	Ustekinumab	Adalimumab	BSC
5	Etanercept	Ustekinumab	Secukinumab	BSC
6	Ixekizumab	Ustekinumab	Secukinumab	BSC
7	Brodalumab	Ustekinumab	Secukinumab	BSC
8	Guselkumab	Ustekinumab	Secukinumab	BSC

The comparator list includes: adalimumab; brodalumab; etanercept; guselkumab; ixekizumab; secukinumab and ustekinumab. Four comparators included in the NICE scope (apremilast, dimethyl fumarate, infliximab and BSC) were not considered to be relevant comparators and were excluded. Apremilast and dimethyl fumarate (DMF) were argued to be positioned in a different part of the NICE psoriasis treatment pathway and were considered to be used either prior to biologic treatments or in patients unsuitable for biologic treatments. Infliximab was not considered a relevant comparator as this is only approved by NICE for patients with very severe psoriasis (PASI≥20 and DLQI>18). BSC was not considered a relevant comparator as it contains no active therapy. Hence, BSC was only included as the final option within each sequence.

The specific sequences were selected based on clinical guidelines and clinical advice received by the company. The company's clinical advisors stated that the three most commonly used interventions are currently adalimumab, secukinumab and ustekinumab. The advisors further stated that secukinumab is becoming more common as a first line therapy and clinicians will rarely switch patients onto a less effective intervention following discontinuation from the first line therapy. The CS also noted that the latest BAD guidelines recommend ustekinumab or adalimumab as a first line biological intervention and that secukinumab should also be considered. [37]

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The tildrakizumab sequence (Sequence 1) was specified as: tildrakizumab > ustekinumab > secukinumab > BSC. The company noted that that NMA results indicated that adalimumab was less effective than tildrakizumab and based on clinical advice it did not consider that adalimumab would be administered after tildrakizumab. The company concluded that the most likely combination post-tildrakizumab would be ustekinumab followed by secukinumab.

The specification of the majority of comparator sequences was based on ensuring consistent comparisons and maintaining a common second and third line treatment. Accordingly, ustekinumab and secukinumab were specified as second and third line options for the majority of comparator sequences (sequence 2 and sequences 5-8). The exceptions to this approach were for the sequences which started with either ustekinumab or secukinumab. Where ustekinumab was included first line, adalimumab was specified as the second line option. Where secukinumab was included first line, adalimumab was specified as the third line option.

The CS acknowledged that not all feasible sequences were included, on the grounds that including all possible permutations would be unwieldy (e.g. 8^3=512 possible permutations). Instead, the justification of the selected sequences was based the company's view of the most clinically plausible combinations and also ensuring that each comparator was included in at least one sequence as a frontline treatment. The CS further stated that their approach was consistent with the two most recent STAs for ixekizumab (TA442) and brodalumab (TA511) and provided a focused analysis.

An additional scenario analysis was also undertaken where each comparator was compared directly to tildrakizumab as part of a one treatment sequence (i.e. after discontinuation from the first treatment in the sequence, patients move straight onto BSC on which they remain until their death).

ERG commentary

The ERG acknowledges that modelling of treatment sequences as opposed to comparison single lines of therapy followed by BSC more appropriately reflects clinical practice and is consistent with the modelling approaches employed in recent NICE appraisals (e.g. TA368, TA442, TA475 and TA511). However, the ERG also notes that previous TAs have also raised questions regarding whether the selected treatments included in the sequences (excluding a new therapy) are representative of current clinical practice. There were also concerns as to whether different positions have been assessed for a new therapy, i.e. 1st, 2nd, or 3rd position in the sequence. Concerns have also been expressed that modelling selective sequences (as opposed to all feasible sequences) could provide misleading estimates of cost-effectiveness, particularly if there are treatments included in a sequence which are not cost-effective themselves (e.g. TA442, TA475 and TA511).

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The ERG notes that the decision to model three active treatments prior to BSC is consistent with recent NICE appraisals (see Table 21 and Table 22). However, differences are also evident across these appraisals in terms of the sequences considered and particularly the specification of the 3rd line biologic treatment.

Table 21: Treatment sequences compared in TA442 (ixekizumab)

Sequence	1st line	2nd line	3rd line	4th line
1A	Ixekizumab	Ustekinumab 90mg	Infliximab	BSC
1B	Adalimumab	Ustekinumab 90mg	Infliximab	BSC
1C	Etanercept	Ustekinumab 90mg	Infliximab	BSC
1D	Infliximab	Ustekinumab 90mg	Adalimumab	BSC
1E	Secukinumab	Ustekinumab 90mg	Infliximab	BSC
1F	Ustekinumab 45mg	Adalimumab	Infliximab	BSC
1G	Ustekinumab 90mg	Adalimumab	Infliximab	BSC

Table 22: Treatment sequences compared in TA511 (brodalumab)

Sequence	1st line	2nd line	3rd line	4th line
1	Brodalumab	Ustekinumab	Secukinumab	BSC
2	Adalimumab	Ustekinumab	Secukinumab	BSC
3	Apremilast	Ustekinumab	Secukinumab	BSC
4	DMF	Ustekinumab	Secukinumab	BSC
5	Etanercept	Ustekinumab	Secukinumab	BSC
6	Infliximab	Ustekinumab	Secukinumab	BSC
7	Ixekizumab	Ustekinumab	Secukinumab	BSC
8	Secukinumab	Ustekinumab	Adalimumab	BSC
9	Ustekinumab	Adalimumab	Secukinumab	BSC

A variety of approaches have been used in recent STAs to explore the potential bias of modelling select sequences, including adding additional sequences to represent different positioning of new treatments (e.g. as 2nd or 3rd line treatment), as well as presenting analyses based only on a single treatment sequence. While the ERG acknowledges the challenges of including all feasible sequences (which include sequences of different lengths and different ordering), the ERG does not consider that the concerns raised in previous NICE appraisals have been fully addressed by the company.

In TA511 (brodalumab), the ERG proposed an alternative approach to inform the cost-effectiveness of alternative sequences based on net-benefit calculations and associated rankings of each individual treatment compared to BSC. The committee concluded in TA511 that "it would consider comparisons

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of individual treatments with best supportive care in its decision-making to account for potential bias from including non-cost-effective comparators in sequences". Hence, the ERG's exploratory analyses (Section 6) include an additional exploratory analysis comparing individual treatments with BSC.

The ERG also considers that the company's approach appears inconsistent in how particular criteria are applied. For example, adalimumab was assumed not to be administered after tildrakizumab following clinical advice that a less effective intervention was unlikely to be selected following discontinuation from the first line therapy. However, the same rationale does not appear to apply to sequences beginning with ustikinumab and secukinumab, where adalimumab is specified as either of second or third line treatment option, despite being less effective than the previous treatment in the sequence.

The ERG's clinical advisor stated that the first line biologic treatment most commonly used in clinical practice is usually ustekinumab, or adalimumab if a patient has PsA. However, he also noted that when a biosimilar version of adalimumab is available in October 2018, it is likely that the majority of new patients will start biological therapy with this biosimilar. He also stated that they would be unlikely to use tildrakizumab as a first line biologic treatment given the more limited evidence and experience with this treatment compared to older biologic therapies. The advisor also disputed the company's claim that secukinumab is increasingly being used as a first line biologic treatment. The ERG's advisor stated that usage of secukinumab tends to be reserved for 2nd or later line use for patients who have failed either adalimumab or ustekinumab, due to experience of higher rates of secondary failure with secukinumab. The advisor also stated that higher efficacy treatments such as ixekizumab and brodalumab are now being commonly used as 3rd line treatments.

The ERG's advisor also questioned the relevance of the BSC comparator as the fourth treatment line. He stated that, in his experience, he hasn't yet had to give up on a biologic route for patients and that increasingly there are fewer patients who are not adequately controlled on biologics. For patients who are only partially controlled on biologics, the end-point is usually a biologic in addition to other treatments, including encouragement for lifestyle improvement.

In Section 2.3, the ERG concluded that apremilast, DMF and infliximab should have been included in the company's decision problem. However, there may also be additional considerations which could justify the exclusion of these treatments from the cost-effectiveness analysis. Although the ERG's clinical advisor acknowledged that the NICE guidance for DMF and apremilast permits use as an alternative to a biologic treatment, he didn't consider that either therapy would be routinely used in this manner; citing concerns regarding lower efficacy of both treatments and concerns that DMF is highly immunosuppressive. The ERG also notes that a similar view was expressed by experts in TA

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419 (apremilast), where it was reported that "the committee understood from the clinical experts that, in general, apremilast would not displace a biological therapy in the treatment pathway. It concluded that the most likely position for apremilast in the treatment pathway was if biological therapies were not tolerated or after all biological therapies had failed". Similarly, a case was also made in TA521 (guselkumab) for excluding apremilast and DMF as relevant comparators. The company submission for TA521 stated that the NICE technical team verbally advised that the cost-comparison case could be made only against alternative biologic treatments. Hence, based on these broader considerations, the company's restriction to only including other alternative biologic treatments appears consistent with recent NICE appraisals.

The ERG's clinical advisor also stated that there is very limited use of infliximab in practice and that usage is mainly confined to severe patients who were managed historically with infliximab prior to the availability of more efficacious treatments such as brodalumab. However, despite the limited use of infliximab, the ERG highlights that infliximab has been routinely included in previous NICE TAs and for completeness should have been included as an alternative biologic comparator.

In conclusion, the ERG considers that there are significant issues with the selective approach used by the company in their sequence comparisons. The ERG notes that the exclusion of DMF and apremilast as comparators appears consistent with recent appraisals. However, the ERG concludes that infliximab should have been included. Additional exploratory analyses to address these issues are presented by the ERG in Section 6.

5.2.5 Perspective, time horizon and discounting

The perspective of the analysis was the NHS and Personal Social Services (NHS & PSS). An annual discount rate of 3.5% was applied to both costs and health effects, in line with NICE guidance. A lifetime horizon (approximately 58 years) was chosen to capture all relevant differences in costs and benefits between comparators. The company noted that the choice of time horizon was partially consistent with previous appraisals where variable time horizons have been employed (e.g. TA103, TA146, TA180 and TA350: 10 years; TA511: 40 years; TA442: lifetime horizon).

ERG commentary

The use of a lifetime horizon is considered appropriate by the ERG and necessary to account for the long-term consequences of a chronic, lifetime disease like psoriasis. However, the ERG also notes that the robustness of the results to alternative time horizons were not presented by the company and considers this to be a potential limitation.

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The ERG also considers that the assumption used for the gender distribution (50:50 male to female ratio) results in a longer lifetime horizon than if the company had based the ratio on the gender distribution reported in the reSURFACE 1 and 2 trials.[5] Despite these concerns, the ERG does not consider that the gender distribution and mortality assumptions introduce any meaningful bias into the cost-effectiveness results. While different gender distributions will impact on the absolute costs and QALYs, the ERG does not consider that this results in any meaningful bias in terms of the incremental estimates which drive the final ICER results.

5.2.6 Treatment effectiveness and extrapolation

The measure of treatment effectiveness used in the model is the proportion of individuals achieving a specific threshold of PASI response where this is judged as the change in severity of psoriasis relative to baseline. Relative change in PASI response based on relative change in severity is the most widely reported outcome in clinical trials and has been used as the main outcome in previous models. The PASI responses during the induction period were based on the company's random effect (not placebo adjusted) NMA described and critiqued in previous sections.

At the end of each induction period patients are allocated to one of the following four health states:

- PASI 0-49: an improvement in their psoriasis less than 50%
- PASI 50-74: an improvement in their psoriasis between 50 and 74%
- PASI 75-89: an improvement in their psoriasis between 75 and 89%
- PASI 90-100: an improvement in their psoriasis between 90 and 100%

The proportion of patients in each PASI category at the end of the induction period are summarised in Table 23 and Table 24. The proportions for tildrakizumab 100mg and 200mg were based on the absolute PASI responses predicted from the NMA. The PASI response categories for each comparator were estimated using the relative risk for each comparator versus either tildrakizumab 100mg or 200mg (Table 25and Table 26)

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Table 23: PASI response rate at week 14 (end of induction period); tildrakizumab 100mg

Treatment	Proportion of patients achieving PASI response		
	≥50	≥75	≥90
Tildrakizumab	[redacted]	66.70%	41.53%
Adalimumab	83.69%	66.04%	40.70%
Brodalumab	96.37%	88.05%	70.19%
Etanercept	66.78%	44.02%	21.18%
Guselkumab	93.83%	83.38%	63.13%
Ixekizumab	96.37%	88.05%	69.78%
Secukinumab	93.83%	84.05%	63.50%
Ustekinumab	85.38%	68.70%	51.90%
BSC	16.06%	6.00%	1.25%

Replication of CS Table 28

Table 24: PASI response rate at week 14 (end of induction period); tildrakizumab 200mg

Treatment	Proportion of patients achieving PASI response		
	≥50	≥75	≥90
Tildrakizumab	[redacted]	69.55%	44.67%
Adalimumab	83.77%	66.07%	40.65%
Brodalumab	95.86%	87.63%	70.13%
Etanercept	66.49%	43.82%	20.99%
Guselkumab	94.13%	83.46%	63.43%
Ixekizumab	95.86%	87.63%	70.13%
Secukinumab	94.13%	84.15%	63.50%
Ustekinumab	85.49%	68.85%	51.90%
BSC	15.54%	5.56%	1.34%

Replication of CS Table 29

Table 25: Relative risk for each comparator versus tildrakizumab 100mg

Treatment	Relative risks of achieving PASI response (95% CrI)		
	≥50	≥75	≥90

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Adalimumab	[redacted]	[redacted]	[redacted]
Brodalumab	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]
Guselkumab	[redacted]	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]

Adapted from CS Tables 30 and 38; p100 & p112-113

Table 26: Relative risk for each comparator versus tildrakizumab 200mg

Treatment	Relative risks of achieving PASI response (95% CrI)		
	≥50	≥75	≥90
Adalimumab	[redacted]	[redacted]	[redacted]
Brodalumab	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]
Guselkumab	[redacted]	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]

Adapted from CS Tables 31 and 38; p101 & p112-113

The PASI 75 response rate was selected as the response threshold for treatment continuation beyond the induction period. The company justified this choice by stating that the decision rule was aligned with previous NICE appraisals. Accordingly, patients who achieved a change in PASI of ≥75 at the end of the induction period were defined as responders and assumed to remain on the same treatment during the maintenance period. Patients who achieved a PASI change of <75 were defined as non-responders and assumed to move into the induction period of the subsequent treatment in the sequence.

In the base-case analysis, it was assumed that prior biologic treatment did not modify treatment response and that the effectiveness of a drug was independent of its position in a sequence. Although the company noted that PASI response may be lower when a treatment is given as second or third line, they also argued that the evidence for this appear variable. The company reported contradictory findings from several studies regarding the possible association between time on treatment (drug survival) and prior exposure to biologic therapies. The company also noted that the approach was aligned with the assumptions used in previous NICE submissions and since the same assumption is

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applied across all the treatments included within the analysis, it was not expected to be a significant driver of the cost-effectiveness results.

ERG commentary

The company's base case analysis uses the Stage I network (12-16 week time point) which does not include the infliximab trials. The company used the best fitting statistical model for this network; the random-effect model without placebo adjustment.

As previously discussed in Section 4.4, the ERG considers that the most appropriate network is the Stage I network including the infliximab trials. The model fit statistics (Table 60 of clarification response) indicate that the RE model without placebo adjustment is the best fit.

The robustness of the cost-effectiveness results to the ERG's preferred network and using the RE placebo adjusted model is considered in Section 6.

5.2.7 Discontinuation rates

A constant annual discontinuation rate of 18.7% was applied in the maintenance period to all treatments (except BSC). This rate includes drop-outs for any reason (loss of response, adverse events, etc.). This rate was based on the approach used in TA511 (brodalumab). In TA511, an 18.7% discontinuation rate was obtained by applying an exponential model to registry data from BADBIR using data from years 2 and 3. [8] This annual discontinuation was then converted to a 14 week probability (4.67%) and applied at each cycle during the maintenance period.

Although the company acknowledged that discontinuation rates may vary depending on the chosen intervention, they considered that there were insufficient data to permit the inclusion of treatment-specific discontinuation rates in the base-case analysis. The company noted that the only available data source for a number of treatments (including tildrakizumab) were RCTs and that, due to the strict protocols applied, the rates of discontinuation may not reflect clinical practice. As a result, the company proposed a scenario analysis using registry data for the more established treatments (etanercept, adalimumab, ustekinumab and secukinumab) to explore the robustness of alternative treatment discontinuation assumptions.

The company's scenario analysis used data from the Danish Biologic Interventions Registry (DERMBIO) for the four of the biologic treatments (adalimumab, etanercept, ustekinumab and secukinumab). [9] The company justified the use of data from DERMBIO rather than from the UK-specific registry (BADBIR) given the longer time horizon and the existence of published data for secukinumab.[8, 9] The DERMBIO registry is based on mandated data collection from all Danish patients receiving biologic therapies (or biosimilar) for moderate to severe psoriasis. [9] The specific

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study that was used was based on a total of 3,495 treatment series (2,161 patients) with data collected over a 10-year period (2007-2017). The number of treatment series available for each treatment was: adalimumab n = 1332; etanercept n = 579; infliximab n = 333; ustekinumab n = 1055 and secukinumab n = 196. Although treatment series data were also reported for infliximab (n=333), these were not included given that the company did not consider infliximab to be a relevant comparator.

The CS reported limited details on the data and approach used to estimate annual discontinuation rates from DERMBIO. [9] The company stated that they fitted separate exponential curves to each treatment based on the published drug survival data. The CS stated that the first four months of data were excluded from the curve fitting to avoid double counting discontinuations already accounted for in the model during the initial induction period. Based on fitted exponential curves, the company estimated the following constant annual probabilities:

- Adalimumab = 8.20%
- Etanercept = 16.10%
- Secukinumab = 49% (subsequently assumed in model to be 7.9%)
- Ustekinumab = 7.90%

The CS noted that the fitted exponential curves for secukinumab predicted an annual discontinuation rate of 49%. However, given the magnitude of difference compared to the other treatments, the company stated that they employed a conservative approach by assuming the same discontinuation rate as estimated for ustekinumab (7.9%).

No equivalent registry data were identified for tildrakizumab, ixekizumab, brodalumab and guselkumab. Since all of these treatments are IL-inhibitors, the company assumed that the discontinuation rate would be more similar to that reported in DERMBIO for the IL-inhibitors (ustekinumab and secukinumab) than those reported for the anti-TNF inhibitors (adalimumab and etanercept). [9] Therefore, the company assumed the same discontinuation rate (7.9%) for all IL-inhibitors, including tildrakizumab.

ERG commentary

The ERG considers the company's approach to discontinuation rates in the base-case to be reasonable and generally consistent with previous appraisals. The ERG notes that the same assumption was used in TA511. However, in TA511 it was noted that the annual discontinuation rate of 18.7% was marginally lower than the rate of 20% used in several other TAs. The reason for the difference in TA511 was attributed to the exclusion of first year discontinuation data from BADBIR. The first year

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was excluded to avoid double counting of discontinuation due to primary non-response already accounted for in the model structure. [8]

The discontinuation rate was differentiated by treatment class in a separate scenario analysis. The scenario analysis explored the assumption that the evidence for ustekinumab from DERMBIO might be generalised to a class effect applying to all the IL-inhibitors (i.e. brodalumab, guselkumab, ixekizumab, secukinumab, tildrakizumab and ustekinumab). [9] The company proceeded to estimate separate discontinuation rates for the IL-inhibitors using a separate exponential model fitted to the ustekinumab drug survival data reported in the DERMBIO registry. [9] Data for the anti-TNFs (adalimumab and etanercept) were based directly on the drug survival data for each individual treatment (8.2 % for adalimumab and 16.1% for etanercept).

The ERG notes several issues and uncertainties regarding the scenario proposed by the company:

- Although the company provided justification for using data from DERMBIO compared to a UK-specific registry (BADBIR), the ERG would have liked to have seen a discussion of any differences that might arise from using BADBIR and consideration of any implications for the scenario proposed by the company.[8, 9] However, the ERG notes that the findings from DERMBIO and BADBIR appear consistent in reporting a substantially lower rate of discontinuation for ustekinumab compared with anti-TNF therapies (adalimumab, etanercept and infliximab). [9] [8]

- The approach assumed a class effect for the IL-inhibitors but allowed differences between anti-TNF treatments. Given the reported differences between anti-TNF treatments, it might be reasonable to assume that differences between the IL-inhibitors may also become evident when longer term follow up data emerges for the individual treatments. This is further supported by the observed difference between ustekinumab and secukinumab in the DERMBIO study (7.9% vs. 49%).[9]

- The ERG also notes that one of reasons given for using DERMBIO in preference to BADBIR was the availability of data for two alternative IL-inhibitors: ustekinumab and secukinumab. However, despite important differences in the annual rate of discontinuation reported between secukinumab and ustekinumab, the company subsequently assumed the same rate for secukinumab as estimated for ustekinumab (i.e. 7.9%).[8, 9] No rationale or justification was provided by the company. Instead, the company simply noted the discrepancy and subsequently stated that they corrected for this using a conservative assumption for secukinumab. The ERG considers that this assumption was not adequately justified by the company and that significant uncertainties remain regarding potential differences in the reported discontinuation rate for ustekinumab and secukinumab and

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the subsequent assumption of a class-effect for all IL-inhibitors. The ERG also notes that there may be appropriate grounds for not using the observed data for secukinumab directly given the shorter follow-up and higher proportion of biologic experienced patients receiving secukinumab in the DERMBIO registry. [9] However, neither of these reasons were highlighted or discussed by the company and no attempt was made to try to control for these potential differences.

- Only limited details were reported by the company in terms of the approach to curve fitting. Neither visual assessments of the resulting fit or goodness of fit statistics were reported by the company to determine that the exponential distribution was the most appropriate distributional assumption.

The ERG considers that there are significant uncertainties surrounding the appropriateness of assuming identical discontinuation rate for all treatments. However, the ERG also acknowledges that generating robust estimates to inform treatment specific comparisons is also problematic given the different data available for particular treatments and the potential confounding in the registry data (e.g. due to differences in the follow-up duration and patient characteristics). The ERG also notes that the use of identical discontinuation rates has been commonly used in previous NICE TAs.

The evidence emerging from longer-term follow up from DERMBIO and BADBIR appear consistent in demonstrating a lower risk of drug discontinuation for ustekinumab compared to other anti-TNF treatments. [8, 9] However, there remains significant uncertainties concerning whether this finding can be generalised to other IL-inhibitors using a class-effect assumption.

5.2.8 Adverse events

Adverse events were excluded from the model. The company justified this decision based on the low rate of adverse reactions in the tildrakizumab studies. This finding was also considered to be consistent with experience for other biologic psoriasis treatments. Given the low incidence of adverse events for tildrakizumab and the biologic comparators, the company did not consider that their inclusion would have any meaningful impact on the results of the analysis.

5.2.9 Health related quality of life

Outcomes of the model were expressed using quality adjusted life years (QALYs). The utility values used in the model were derived from EQ-5D-3L data collected as an exploratory endpoint in the reSURFACE 1 trial at baseline and week 12 Utility estimates were stated to have been derived using the European valuation set for EQ-5D-3L for the patient subgroup with a DLQI>10 (n=482). [5]

Estimates were pooled across all three arms of the resurface 1 trial (i.e. 100mg tildrakizumab, 200mg tildrakizumab and placebo) at baseline and each PASI response categories (<50, 50-75, 75-90, ≥90). [5]

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The utility values in the model (Table 27) were based on the proportion of individuals in the different PASI response categories (<50, 50-75, 75-90, ≥90) and the change in utility from baseline associated with the PASI response category. The same PASI-specific utilites were applied to each model comparator. The utility values during the induction period for each treatment are based on the PASI response categories (PASI <50, PASI 50-74, PASI 75-89, PASI ≥90) assessed at the end of the induction period, i.e. patients immediately achieve the HRQoL associated with their PASI response. Upon entry to the BSC state, patients are distribued to PASI response categories and associated HRQoL according to the placebo response rates estimated using the NMA. Patients remain in this state until the end of the model time horizon or death.

Table 27: Summary of utility values (DLQI>10)

State	Utility change: mean	Final utility value	Source
Baseline	[redacted]	[redacted]	reSURFACE 1[5]
PASI score: <50	[redacted]	[redacted]	
PASI score: ≥50 to <75	[redacted]	[redacted]	
PASI score: ≥75 to <90	[redacted]	[redacted]	
PASI score: ≥90	[redacted]	[redacted]	

CS Table 33, p106

Given the lifetime horizon, the company proposed an adjustment to the utility values to account for the impact of ageing in the model. Hence, rather than applying the utility values directly in the model, the company estimated the percentage change in utility for each PASI category compared to an age-matched population norm value for EQ-5D-3L (0.871; mean age 46). Table 28 summarises the percentage utility change assumed in the company base case model.

Table 28: Summary of percentage change in utility value by PASI response

State	Population norm (age 46)	Utility change: mean	Utility change: percentage
PASI score: <50	[redacted]	[redacted]	[redacted]
PASI score: ≥50 to <75		[redacted]	[redacted]
PASI score: ≥75 to <90		[redacted]	[redacted]
PASI score: ≥90		[redacted]	[redacted]

CS Table 34, p106

ERG commentary

The ERG identified a number of significant concerns regarding the utility data and assumptions used in the company's cost-effectiveness analysis. The ERG also notes that limited information was provided regarding the statistical approaches used by the company to derive these estimates. Basic

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descriptive statistics for the EQ-5D endpoint (e.g. sample sizes, missing data, follow up points, EQ-5D scores at baseline and follow up for each treatment) were also not provided. Although further details were referenced to a separate appendix (Appendix M), no details of the EQ-5D results were provided.

During the clarification stage, the ERG requested descriptive statistics and further details of the regression methods used to estimate change in EQ-5D from baseline to week 12, including confirmation of whether any adjustment was made for baseline EQ-5D and/or other covariates.

The ERG also did not consider that the valuation approach used by the company was in accordance with the NICE reference case. Utility values were stated to have derived from the European value set for EQ-5D-3L rather than the UK value set. The ERG notes that the European valuation set is based on survey data from six Western European countries (Finland, Germany, The Netherlands, Spain, Sweden and the UK) with valuations based on EQ-5D visual analogue scale (VAS) scores. In contrast, the valuations from the UK value set are derived using time-trade off (TTO) approach. During the clarification stage, the ERG requested the company to revise the EQ-5D analyses using index utility estimates based on the UK value set.

The ERG also identified a number of additional issues and concerns regarding the company's proposed adjustment to the utility values to account for the impact of ageing in the model:

- A programming error was identified meaning that utility changes (mean and percentage change) were incorrectly estimated. The estimates applied in the company base case and the corrected estimates are summarised in Table 29.
- The proposed adjustment for ageing assumes a constant multiplicative (i.e. proportional) relationship between age and the impact of each PASI category. The appropriateness of assuming a multiplicative rather than an additive relationship was not discussed in the CS.
- The categorical estimates of UK population norms reported by Kind et al (10 year age bands and for all patients age 80+) were not used directly.[40] Instead, an annual linear decrement was estimated based on the utility differences reported between the categorical age bands and this was used to estimate utilities for yearly age bands. The rationale for this adjustment was not explained and the ERG considers that the way this was implemented imposed further assumptions that were not discussed.
- No further utility decrements for ageing were assumed beyond age 76. It was unclear whether this was an intentional assumption or a separate programming error.

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Table 29: Corrected estimates for percentage change in utility value by PASI response

		Company base case		Corrected estimates	
State	**Population norm (age 46)**	**Utility change: mean**	**Utility change: percentage**	**Utility change: mean**	**Utility change: percentage**
PASI score: <50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI score: ≥50 to <75		[redacted]	[redacted]	[redacted]	[redacted]
PASI score: ≥75 to <90		[redacted]	[redacted]	[redacted]	[redacted]
PASI score: ≥90		[redacted]	[redacted]	[redacted]	[redacted]

Adapted from CS Table 34, p106

Although the ERG recognises the company's efforts to incorporate the impact of ageing with the utility calculations, the subsequent errors and additional assumptions that were imposed raise issues concerning the validity of the base case results and the robustness of the model to alternative assumptions (e.g. additive relationship, alternative ways to estimate linear decrements with age etc.). More importantly, the ERG does not consider that an adjustment for age is necessary. An analysis without ageing would only introduce bias into the incremental calculation where a differential mortality effect is assumed between treatment sequences and/or sequences of different length are considered. Since neither applies to the company base-case, the ERG concludes that the proposed age-adjustment is not correctly implemented and is unnecessary.

Finally, the ERG notes that the use of the DLQI>10 subgroup is not consistent with the use of the ITT population from the NMA which is used to estimate PASI responses. Although the ERG acknowledges that a similar approach has been used in recent NICE appraisals and has been considered to be appropriate, the ERG would have preferred to see the results presented for the full population as well as for this specific subgroup.

During the clarification stage, the company were asked to provide further details on the regression methods used to estimate the change in EQ-5D from baseline to week 12 and to confirm whether any adjustments were made for baseline EQ-5D and/or other covariates. The company were also requested to update their analyses using the UK value set and to present results for the following additional analyses:

a) Results for the full population and for the subgroup with baseline DLQI > 10.

b) Results for PASI 90-99 and PASI 100 (full population and DLQI subgroup).

c) Results for a) and b) adjusting for baseline-EQ-5D score.

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In their response, the company stated that they had incorrectly reported that the European valuation set had been used. The company clarified that the appropriate UK value set was used for all non-USA patients but USA valuations had been used for all patients from the USA. The company provided revised utility results and the results of a scenario showing that the revised results provided cost-effectiveness results that were similar to the base case analysis.

Table 30 compares the original utility values (UK values for non-USA patients and USA values for USA patients) and the revised estimates (UK values for all patients). The company stated that the revised estimates were very similar to those applied in the original base case analysis with the main difference being a small increase in the utility for PASI <50 patients from [redacted].

Table 30 Summary of utility values (DLQI>10) – original and revised estimates

	Original estimates		Revised estimates		
State	**Utility change: mean**	**Utility value**	**Utility change: mean**	**Utility value**	**Source**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	reSURFACE 1[5]
PASI score: <50	[redacted]	[redacted]	[redacted]	[redacted]	
PASI score: ≥50 to <75	[redacted]	[redacted]	[redacted]	[redacted]	
PASI score: ≥75 to <90	[redacted]	[redacted]	[redacted]	[redacted]	
PASI score: ≥90	[redacted]	[redacted]	[redacted]	[redacted]	

The company response also clarified that regression models had not been used to analyse EQ-5D and the utility estimates were based on descriptive statistics only. The company stated that this was consistent with the statistical protocol for the reSURFACE 1 trial since EQ-5D was an exploratory endpoint. [5] Although the company also provided additional analyses in their response using ordinary least squares regression (with EQ-5D score at baseline as a covariate), unfortunately the company misunderstood the clarification question and hence did not provide the results requested.

Although the ERG considers that the company should have used regression models to analyse EQ-5D, it does not consider that this is a major concern. Table 31 compares the revised utility values used by the company with those identified in a recent review of psoriasis treatments by the Institute for Clinical and Economic Reviews (ICER), a U.S. based health technology assessment group.[41] The table shows that the company's revised results appear consistent with estimates reported for other targeted therapies.

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Table 31 Comparison of revised utility estimates (company revised results and ICER review estimates)

State	Utility value	Source	Utility value	Source
Baseline	[redacted]	reSURFACE 1[5]	0.66*	ICER review (average values for immunomodulation therapies) [41]
PASI score: <50	[redacted]		0.72	
PASI score: ≥50 to <75	[redacted]		0.83	
PASI score: ≥75 to <90	[redacted]		0.86	
PASI score: ≥90	[redacted]		0.90	

*Value for non-targeted treatment

Although the company's utility estimates appear appropriate to be considered by the committee for decision making purposes, the ERG notes that the difference between the baseline utility and the utility value for the alternative PASI response states were not discussed by the company. The ERG highlights that the baseline utility estimate is not used in the model. Instead, the model only uses the % utility changes for each of the 4 PASI response states and applies these changes to UK population utility norms. This is important as the minimum reference point for these calculations is [redacted] (PASI<50). Although this might be an appropriate assumption to use while patients are receiving biological therapies, eventually all patients in the model will move to the final treatment state with BSC. The ERG considers that there are significant uncertainties concerning whether these values can be generalised to patients not receiving biological therapies. The ERG explores this issue further in their exploratory analysis and demonstrates that this is an important area of uncertainty.

5.2.10 Resources and costs

The resource use and costs included in the model comprised drug acquisition, administration, monitoring and BSC.

Drug acquisition costs

Table 32 provides a summary of the treatment acquisition costs used in the company's base case. The ERG identified several discrepancies between the table presented in the CS (Table 35) and the Excel model. These discrepancies were checked by the ERG and several amendments were made to the table to address apparent transcription errors. Hence, Table 32 reports the actual costs used by the company in their base-case analysis. Estimates for infliximab were provided in the company's response to points for clarification.

The acquisition cost of tildrakizumab is based on the company's Patient Access Scheme (PAS).The costs for all the comparators were sourced from the list prices reported in the British National Formulary (BNF).[42] The CS does not include the confidential PAS schemes which have been

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approved for brodalumab, guselkumab, ixekizumab and secukinumab. Assuming the NHS would give priority to a biosimilar where available, the lower cost biosimilar for etanercept (and infliximab in the response) was used in the base case.

The induction period cost for tildrakizumab and for all the comparators was based on a common 14 week stopping rule. The CS also stated that adjustments were made to the induction dose and the maintenance dose to ensure that the correct dose was assumed for a 14-week period.

Table 32 Summary of treatment acquisition costs – company estimates**

Drug	Unit cost (£)	Units	Dose per unit (mg)	Trial dose (mg)	Maintenance dose (mg)	Induction period cost*	Maintenance period cost*
Tildrakizumab	[redacted]	1 or 2†	100	400	233	[redacted]	[redacted]
Etanercept (biosimilar)	£322	4	25	700	700	£2,252	£2,252
Adalimumab	£704	2	40	360	280	£3,169	£2,465
Ustekinumab	£2,147	1	45	90	52.65	£4,294	£2,512
Secukinumab	£1,219	2	150	2100	967	£8,532	£3,927
Ixekizumab	£1,125	1	80	640	280	£9,000	£3,938
Brodalumab	£1,280	2	210	1680	1470	£5,120	£4,480
Guselkumab	£2,250	1	100	300	188	£6,750	£4,230
Infliximab	£377	1	100	1500	875	£5,655	£3,299

*Costs shown correspond to a 14 week model cycle, which may be different to the length of a treatment cycle in routine clinical practice.
†Either 1 or 2 100mg tildrakizumab doses will be administered depending on the required dose (i.e. patients on the 200mg dose will receive two 100mg doses instead of one[redacted]
** Induction and maintenance costs corrected by ERG to deal with transcription errors included by company reporting in Table 35 (CS)

In Section 5.2.3, the ERG raised concerns regarding the potential bias introduced by assuming a common induction period for all treatments, rather than using the recommended induction periods. To determine the magnitude of this bias, the ERG estimated the induction period cost for the comparators using the correct induction periods aligned with NICE guidance. No adjustment was made the HRQoL estimates druing the induction periods. The ERG also checked the source of the unit cost estimates and the company's adjustments for the 14-week maintenance period costs.

Table 33 summarises the ERG's preferred estimates for the induction and maintenance period. Differences in the induction period are due to the ERG basing the induction cost on the recommended time period for the assessment of response for the comparators, rather than assuming a common 14-week assessment period. However, differences are also evident in the maintenance period which is based on a 14-week cycle for tildrakizumab and all the comparators.

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Table 33 Summary of treatment acquisition – ERG revised estimates

Drug	Unit cost (£)	Units	Dose per unit (mg)	Trial dose (mg)	Maintenance dose (mg)	Induction period cost*	Maintenance period cost*
Tildrakizumab	[redacted]	1 or 2†	100	200/400	-	[redacted]	[redacted]
Etanercept (biosimilar)	£322	4	25	600	-	£1,931	£2,252
Adalimumab	£704	2	40	400	-	£3,521	£2,465
Ustekinumab	£2,147	1	45	90	-	£4,294	£2,503
Secukinumab	£1,219	2	150	1800	-	£7,313	£3,938
Ixekizumab	£1,125	1	80	560	-	£7,875	£3,938
Brodalumab	£1,280	2	210	1470	-	£4,480	£4,480
Guselkumab	£2,250	1	100	300	-	£6,750	£3,938
Infliximab	£377	1	100	1500	875	£5,655	£3,299

*Costs shown correspond to the actual induction period specified in previous NICE guidance
†Either 1 or 2 100mg tildrakizumab doses will be administered depending on the required dose (i.e. patients on the 200mg dose will receive two 100mg doses instead of one[redacted]

The reason for the difference in maintenance costs appears to be due to the different assumptions made by the company and the ERG to adjust to the 14-week cycle length of the model. The company stated that adjustments were made to the dose assumptions when the administration schedule did not align exactly with the 14-week cycle. The ERG's approach estimated the annual maintenance cost of each treatment and then converted this to a 14-weekly cost equivalent (i.e. 14/52 * annual cost). For example, guselkumab is administered every 8 weeks. The ERG estimated the annual cost (based on list price) as £14,625 (i.e. 6.5 doses [52/8]*£2,250), which resulted in a 14-week equivalent cost of £3938 (i.e. 14/52*£14,625). The ERG was unclear how the company adjusted the doses in their maintenance estimates as the calculations were not provided in the Excel model. However, the ERG notes that the implied annual cost of guselkumab using the company's approach is £15,711. This is over £1,000 per year higher than the ERG's calculations. The ERG is unclear whether there is any valid reason for this difference.

The ERG considers that the model should accurately reflect the induction periods recommended for each comparator. The ERG was also not able to replicate the company's maintenance cost estimates. As a result, the ERG states a strong preference for using the ERG's revised inputs.

Administration costs

The company's base case does not include administration costs. All the treatments included in the company base case are given via self-administration subcutaneous injections. Although the company notes that there may be a small cost associated with self-administration (e.g. training by a nurse), this

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would be incurred once to all patients at initiation of the first treatment in the sequences. As a result, the administration cost would be the same across all sequences and would not impact the incremental cost estimates.

The ERG notes that the inclusion of administration costs for subcutaneous treatments has been variable across previous NICE TA. For example both TA442 (ixekizumab) and TA350 (secukinumab) include nurse training cost for self-administration during the induction period. In TA442, a total administration cost of £108 was assumed, representing the cost of three 1-hour training sessions with a nurse. However, TA511 (brodalumab) did not include these costs.

The ERG report for TA511 also highlighted that the provision and funding of homecare delivery services by companies often also include provision of home training. Hence, there exists some uncertainty about whether any administration costs for subcutaneous treatments are incurred by the NHS or not. For completeness (and to address the scenario in which infliximab is included as a comparator), the ERG would have liked to have seen these costs included. However, the impact of their inclusion/exclusion is not considered by the ERG to have any material effect on the cost-effectiveness results.

Monitoring costs

Resource use for monitoring during the induction and maintenance period was assumed to be similar for all treatments. The frequency of monitoring was based on NICE CG153 and were reported to be aligned with guidance from BAD. [8] Unit costs were sourced from the 2016/17 NHS Reference Costs. Resource use and cost assumptions are provided in the CS (Table 36).[43]

The ERG considers these estimates to be appropriate.

Non-responder costs

The company base case does not include any additional healthcare costs for patients who fail to respond to biologics and switch to another treatment or BSC. The ERG notes that several NICE TA appraisals have included 'non-responder' costs within their base-case analyses and these additional costs were considered justifiable by the ERGs and previous committees. The exclusion of these costs from the company's base case appears to be an optimistic assumption for tildrakizumab compared to treatments with a higher PASI75 response.

As part of the points for clarification, the company were requested to present a scenario analysis incorporating additional costs for non-responders in line with other NICE TAs. In their response, the company provided an additional scenario including an additional cost of £229 which was assumed to be incurred once per treatment line during the induction cycle for all patients who achieve a PASI <75

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response. This cost was based on a figure of £225 per cycle used in TA442 and TA475, inflated to a 2016/17 price year.

The ERG considers that non-responder costs should be included. However, the ERG do not agree with the proposed estimate of £229. The estimate of £225 is based on a 4 week cycle length reported in TA442. This was subsequently adjusted by the ERG in TA475 to reflect the cost of a 2 week cycle length (see paragraph 3.17, TA475 Final Appraisal Document). Hence, although proposed unit cost estimate is consistent with previous appraisals, this unit cost needs to be adjusted to the 14 week cycle length for this appraisal. Hence, the ERG concludes that the appropriate estimate for the cost of non-response should be £801.50 (i.e. £229*14/4).

BSC costs

The cost of BSC in the company's base case was based on estimates used to inform NICE CG153. The CS also noted that two of the most recent NICE submission (TA 442 and TA511) used an alternative estimate reported by Fonia et al (2010).[44] The estimates reported by Fonia are based on a retrospective UK-based observational study of 76 patients with moderate to severe psoriasis who had been referred to a tertiary severe psoriasis service and subsequently completed 12 months of biologic therapy.[44]

The company's advisers considered that the study by Fonia et al. no longer represents UK clinical practice for BSC and underestimates the cost for this treatment (see company response document, p88).[44] Hence, the company preferred to use estimates from NICE CG153 for their base case analysis, as this was the only alternative identified and the overall cost was higher than the reported by Fonia. The company also presented a separate scenario using the estimates reported by Fonia et al.[44]

Table 34 summarises the resource use and cost assumptions used for BSC in the company base case. The base case assumes a per-cycle (14 weeks) cost of £3,088. The equivalent per-cycle cost based on Fonia et al was £1,422.[44]

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Table 34 Best supportive care costs and resource use in company base case (CA Table 37 (p111)

Items	Resource use	Average annual cost	Cost per cycle
Drugs			
Methotrexate	Proportion of patients = 45% Frequency per year = N/A	£191	£51.41
Ciclosporin	Proportion of patients = 45% Frequency per year = N/A	£1,122	£302.16
No drug (outpatient visits)	Proportion of patients = 10% Frequency per year = 5.00	£32	£8.49
Other treatment			
Day care centre (visits)	Proportion of patients = 100% Frequency per year = 5.00	£1,906	£513.07
Narrow-band UVB (sessions)	Proportion of patients = 16% Frequency per year = 24.00	£316	£85.21
Inpatient care			
High need (admissions)	Proportion of patients = 82% Frequency per year = 1.00	£5,066	£1.363.88
Very high need (admissions)	Proportion of patients = 18% Frequency per year = 2.55	£2,836	£763.44
Total cost		**£11,468**	**£3,088**

The relevance of these alternative sources has been extensively discussed in previous NICE TAs. For example, the FAD documents for TA419 and TA350 report that, while the committee recognised the uncertainty and shortcomings of existing sources for resource use for BSC, the committee also concluded that estimates were likely to be closer to Fonia et al. than to the estimates from NICE CG53. As a result, estimates from Fonia et al. have been used in all subsequent appraisals (for example TA442, TA475, TA511 and TA521). [44]

Based on considerations from previous NICE TAs, the ERG concludes that the estimates reported by Fonia et al (2010) appear more appropriate than the company's base case inputs. [44]

Adverse event costs

The resource use and costs of adverse events were not included in the company's base case. The company cited the low incidence of adverse events for tildrakizumab and other biological comparators and concluded that their inclusion would not result in a meaningful impact on the cost-effectiveness results.

The ERG would have preferred the inclusion of adverse event costs in the base caes analysis. However, they also concur with the company's conclusions that these are not likely to be an important driver of cost-effectiveness and hence would not lead to any major differences in the ICER results.

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5.2.11 Discounting

Costs and outcomes were appropriately discounted at 3.5% in line with NICE recommendations.

5.2.12 Cost effectiveness results

Table 35 summarises the company base-case cost-effectiveness results based on the deterministic analysis. Fully incremental cost-effectiveness ratios (ICERs) and pairwise incremental net monetary benefit (INMB) estimates for the tildrakizumab sequence compared to each comparator sequence, were reported. These results do not include the confidential PAS schemes for brodalumab, guselkumab, ixekizumab and secukinumab. The results of the company base case and the ERG exploratory scenarios including the confidential PAS schemes are reported separately in a confidential appendix to the ERG report.

The results in Table 35 refer to analyses using the 100mg dose for tildrakizumab. The company also presented similar results for the 200mg dose. The ERG notes that there is some uncertainty in terms of which patients may be eligible to receive the 200mg dose: the draft SmPC simply states that tildrakizumab 200mg may provide greater efficacy in patients with certain characteristics (e.g. high disease burden, body weight ≥90kg). The ERG also notes that the differences between the 100mg and 200mg doses appear small and non-significant and show no clear evidence to support differential efficacy based on the PASI and PGA data.

[redacted] the ERG considers that the cost-effectiveness results using the 100mg dose are sufficiently generalisable to the 200mg dose. Hence, and for the sake of brevity, the ERG only summarises results for the 100mg dose.

Following conventional decision rules for cost-effectiveness, the mean costs and QALYs for the various sequences were presented and cost-effectiveness was compared by estimating ICERs as appropriate. The ICER examines the additional costs that one sequence incurs over another (ΔC) and compares this with the additional QALY benefits (ΔE). When more than two sequences are being compared the fully incremental ICERs are calculated using the following process:

i) The sequences are ranked in terms of mean cost (from the least expensive to the most costly).

ii) If a sequence is more expensive and less effective than any previous sequence of lower cost, then this sequence is said to be dominated and is excluded from the calculation of the ICERs.

iii) After excluding any dominated sequences, the ICERs are calculated for each non-dominated sequence, from the cheapest to the most costly. If the ICER for a given sequence is higher than that of any more effective strategy, then this sequence is ruled out on the basis of extended dominance.

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iv) The final ICERs are then recalculated excluding any strategies that are ruled out by principles of dominance or extended dominance.

In the fully incremental ICER comparison, there were 3 non-dominated (dominance and extended dominance) sequences. Of these, the least effective and lowest cost was the sequence starting with tildrakizumab (sequence 1). The ICER of the ixekizumab sequence (sequence 6) was reported to be £155,597 per QALY compared to the tildrakizumab sequence. The brodalumab sequence (sequence 7) was the most effective and most costly of the non-dominated sequences. The ICER of the brodalumab sequence versus the ixekizumab sequence was £2,817,613 per QALY.

The table also presents a pairwise comparison of the INMB of the tildrakizumab sequence compared to each individual comparator sequence. The INMB is estimated by re-arranging the ICER equation and the conventional decision rule for cost-effectiveness ($\Delta C/\Delta E < \lambda$; where λ represents the decision threshold used to determine cost-effectiveness [i.e. £20,000 - £30,000 per QALY]), such that:

$$\textit{Incremental net monetary benefit (NMB)} = \lambda \times \Delta E - \Delta C$$

In contrast to conventional ICER decision rules, the net-benefit approach provides an unambiguous decision rule. If an intervention has an incremental NMB or NHB>0 at a specific λ, then the intervention is considered to be cost-effective. At a £20,000 threshold, the tildrakizumab sequence generated a positive NMB versus each individual comparator sequence.

The company concluded that results showed that the tildrakizumab sequence (sequence 1) was the most cost-effective option at a cost-effectiveness threshold of £20,000 and £30,000 per QALY gained.

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Table 35: Company base case deterministic results – tildrakizumab 100mg

Sequence	1st line	2nd line	3rd line	4th line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) fully incremental	INMB (£/QALY) TIL sequence versus comparator
1	TIL	UST	SEC	BSC	[redacted]	[redacted]	£0	0	-	N/A
5	ETA	UST	SEC	BSC	£236,523	[redacted]	[redacted]	[redacted]	Dominated	£4,034
2	ADA	UST	SEC	BSC	£237,059	[redacted]	[redacted]	[redacted]	Dominated	£1,043
3	UST	ADA	SEC	BSC	£237,822	[redacted]	[redacted]	[redacted]	Dominated	£1,794
4	SEC	UST	ADA	BSC	£245,952	[redacted]	[redacted]	[redacted]	Extendedly Dominated	£9,760
6	IXE	UST	SEC	BSC	£265,026	[redacted]	[redacted]	[redacted]	£155,597	£25,177
8	GUS	UST	SEC	BSC	£265,095	[redacted]	[redacted]	[redacted]	Dominated	£26,075
7	BRO	UST	SEC	BSC	£267,202	[redacted]	[redacted]	[redacted]	£2,817,613	£27,337

Replication of table (CS Table 40), p116. Abbreviations: ADA: adalimumab; BRO: brodalumab; BSC: best supportive care; ETA: etanercept; GUS: guselkumab; ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; IXE: ixekizumab; N/A: not available; QALY: quality-adjusted life year; SEC: secukinumab; TIL: tildrakizumab; UST: ustekinumab.

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5.2.13 Sensitivity analysis

The company presented the uncertainty in the model in three alternative ways: a probabilistic sensitivity analysis (PSA), a series of one way deterministic sensitivity analyses (DSA) and a series of scenarios.

Probabilistic sensitivity analysis

The company performed a PSA where the input parameters were sampled probabilistically from distributions based on 1,000 simulations. Full details of the PSA inputs and associated distributions are reported in the CS (Table 42, p120).

Table 36 summarises the company base-case cost-effectiveness results based on the probabilistic analysis. Fully incremental ICERs and pairwise INMB for the tildrakizumab sequence compared to each comparator sequence were reported.

In the fully incremental ICER comparison, there were two non-dominated sequences. Of these, the least effective and lowest cost was the sequence starting with tildrakizumab (sequence 1). The ICER of the ixekizumab sequence (sequence 6) was reported to be £152,838 per QALY compared to the tildrakizumab sequence.

The company concluded that PSA results also demonstrated that the tildrakizumab sequence (sequence 1) was the most cost-effective option at a cost-effectiveness threshold of £20,000 and £30,000 per QALY gained.

ERG comments

The ERG has several concerns regarding the PSA. Firstly, the model is only capable of comparing two sequences simultaneously. Hence, the results of the PSA comparing all the sequences (Table 43 and Figure 24; CS) appear to have been derived from separate model runs where the tildrakizumab sequence is compared against each individual comparator sequence. This approach results in different random seeds for each model run, increasing 'noise' in the simulation because different values are likely to be drawn within each simulation for common parameters. Although this approach is unlikely to generate any obvious bias, it may require a greater number of simulations to generate robust estimates of the mean costs and QALYs. The ERG notes that the company only ran 1,000 simulations and did not assess the robustness of the results when the number of simulations was increased.

Secondly, assigning independent distributions to the treatment effectiveness parameters (see CS Table 42, p120) ignores the correlation between the efficacy inputs (PASI50, PASI75 and PASI90 response rates) and between individual treatments. The correct approach would have been to sample directly from the posterior distributions obtained from the NMA (using the WinBUGS CODA), ensuring that

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the correlation is maintained in the PSA. As a result, the ERG does not consider that the uncertainty surrounding the effectiveness inputs has been appropriately characterised and propagated in the model.

In response to the points for clarification, the company submitted an updated the model in which the PASI outcomes were directly informed by the WinBUGS CODA with a sample of 3,000 iterations run.

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Table 36: Company base case probabilistic results – tildrakizumab 100mg

Sequence (first treatment only shown)	Total QALYs		Total costs		Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator)
	Mean	95% Crl	Mean	95% Crl		
1: Tildrakizumab	[redacted]	[redacted]	[redacted]	[redacted]	-	N/A
5: Etanercept	[redacted]	[redacted]	£235,852	£187,866 to £294,067	Dominated	£3,984
2: Adalimumab	[redacted]	[redacted]	£236,226	£192,220 to £293,501	Dominated	£943
3: Ustekinumab	[redacted]	[redacted]	£238,647	£192,960 to £297,713	Dominated	£1,786
4: Secukinumab	[redacted]	[redacted]	£247,121	£200,895 to £299,296	Dominated	£9,745
8: Guselkumab	[redacted]	[redacted]	£264,749	£221,552 to £314,659	Extendedly Dominated	£26,085
6: Ixekizumab	[redacted]	[redacted]	£266,268	£220,639 to £316,947	£152,838	£25,060
7: Brodalumab	[redacted]	[redacted]	£267,522	£225,342 to £316,493	Dominated	£27,292

Replication of table (CS Table 43), p122. Abbreviations: Crl: credible interval: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; N/A: not available; QALY: quality-adjusted life year

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Deterministic sensitivity analysis

The CS reported the results of a variety of one-way deterministic sensitivity analyses (DSA) to identify the key drivers of the cost-effectiveness model. Treatment effectiveness and utility parameters were varied with the 95% confidence interval and all other parameters were varied by +/- 50% of the base case value.

The CS presented a series of tornado diagrams depicting the results of the DSA (Figure 26-Figure 32 CS) in terms of the INMB of the tildrakizumab sequence compared to each individual comparator sequence. The tornado diagram demonstrated that the parameters with the largest influence on the INMB were: (i) the unit costs of tildrakizumab; (ii) the discontinuation rate of tildrakizumab and/or the comparator sequence; (iii) the costs of BSC and (iv) PASI 75 response outcomes for tildrakizumab and/or the comparator sequence.

The ERG considers that the DSA are useful in terms of identifying the main cost-effectiveness drivers, specifically the PASI response outcomes, the costs of BSC and the discontinuation rate. The ERG does not consider it appropriate to use DSA to assess the impact of alternative unit cost estimates for tildrakizumab, as the price and PAS are known.

Scenario analysis

The submission also included an extensive series of scenario analyses to check the robustness of the model results to alternative structural assumptions and data sources. A summary of the scenarios and results is reported in Table 37.

The company concluded that the results of the base case analysis were robust as there appeared limited impact on the overall conclusions from the majority of scenarios. However, the company identified one specific scenario in which the tildrakizumab sequence was no longer the most cost-effective sequence. This was the sequence when the costs of BSC were derived from Fonia et al rather than NICE CG53. [44] In this scenario, the etanercept sequence was the least costly and more cost-effective sequence at a £20,000 per QALY threshold and the tildrakizumab sequence was extendedly dominated. The company noted that at a £30,000 threshold, the tildrakizumab sequence was the most cost-effective sequence and concluded that the cost of BSC was an important driver of cost-effectiveness.

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Table 37: Summary of sensitivity analysis (CS, Table 57)

Scenario number	Feature assessed	Overview of the scenario	Conclusion	Location in CS
1 to 3	Proportion of patients receiving 100mg or 200mg doses	Weighted average of the 100mg and 200mg base case results estimated based on the proportion expected to receive 200mg dose. Three different values examined.	Limited change from base case with the tildrakizumab sequence the most cost-effective option.	p135-139 (Tables 46-48, p138-139)
4	Mortality of population	Increased mortality rate with plaque psoriasis patients, compared with general population, modelled based on hazard ratio of 1.42	Limited change from base case with the tildrakizumab sequence the most cost-effective option.	p140-141 (Table 49, p141)
5	28 week effectiveness data	The effectiveness of each treatment was based on outcomes at 28 weeks, not 12 to 16 weeks	Limited change from base case with the tildrakizumab sequence the most cost-effective option.	p142-143 (Table 50)
6	Relative risk of 1 when insignificant (for efficacy data)	If confidence interval of tildrakizumab crosses 1 at end endpoint (i.e. PASI response) then no difference modelled	Limited change from base case with the tildrakizumab sequence the most cost-effective option.	p144-146 (Table 51, p146)
7	Single treatment comparison	Each comparator was compared directly to tildrakizumab with only one active therapy in each sequence	Limited change from base case with the tildrakizumab sequence the most cost-effective option.	p147-148 (Table 52, p148)
8	BSC cost	Data from Fonia *et al.* used to estimate cost of BSC [44]	Etanercept sequence became the most cost-effective option but with only a small difference compared with tildrakizumab.	p149-150 (Table 53, p150)
9	Discontinuation	Different annual rates of discontinuation applied based on DERMBIO registry data [9]	Limited change from base case with the tildrakizumab sequence the most cost-effective option.	p151-153 (Table 54, p153)
10	Utility data	Different utility values applied in the model based on data identified in the wider literature (majority of sources were previous NICE submissions in this indication).	Limited change from base case with the tildrakizumab sequence the most cost-effective option.	p154-155 (Table 56, p155)

Adapted from CS, Table 57

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Table 38: Scenario results using alternative estimates of the costs of BSC

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
5: Etanercept	£165,118	[redacted]	NA	NA	NA	-£409
1: Tildrakizumab	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	N/A
2: Adalimumab	£170,097	[redacted]	[redacted]	[redacted]	Dominated	£1,022
3: Ustekinumab	£170,860	[redacted]	[redacted]	[redacted]	Dominated	£1,773
4: Secukinumab	£178,995	[redacted]	[redacted]	[redacted]	Dominated	£9,743
8: Guselkumab	£201,639	[redacted]	[redacted]	[redacted]	Extendedly dominated	£29,548
6: Ixekizumab	£202,445	[redacted]	[redacted]	[redacted]	£187,881	£29,550
7: Brodalumab	£204,606	[redacted]	[redacted]	[redacted]	£4,529,076	£31,701

Replication of table (CS Table 53), p150. Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; QALY: quality-adjusted life ye

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The ERG notes that Scenarios 1 to 3 used a weighted average approach which combined the results for the 100mg and 200mg tildrakizumab doses. The three scenarios reflected different weights based on alternative assumptions concerning the proportion of patients who would get the 100mg and 200mg doses. Scenario 1 assumed that the tildrakizumab 200mg dose would only be used in patients >90kg and assumed that [redacted]% and [redacted]% of patients would receive the 200mg and 100mg doses respectively. Scenario 2 assumed the tildrakizumab 200mg dose would only be used in patients with baseline PASI ≥20 and assumed that [redacted]% and [redacted]% of patients would receive 200mg and 100mg doses respectively. Scenario 3 assumed the tildrakizumab 200mg dose would only be used in patients>90kg and with baseline PASI ≥20 and assumed that [redacted]% and [redacted]% of patients would receive 200mg and 100mg doses respectively.

The company reported that the results of the three scenarios were very similar. In all three scenarios tildrakizumab (sequence 1) was the referent comparator sequence (i.e. the cheapest) in the fully incremental analysis. Also, in all three sequences the only non-dominated comparator sequences, ixekizumab (sequence 6) and brodalumab (sequence 7), were more costly and more effective than tildrakizumab (sequence 1), with ICERs of approximately £160,000 for ixekizumab and a range of £3,300,000 and £4,900,000 for brodalumab.

The ERG highlights that the similarity of the scenarios is to be expected given the small and non-significant differences between the 100mg and 200mg doses. The ERG also considers that the similarity reinforces their view that the cost-effectiveness results using the 100mg dose are sufficiently generalisable to the 200mg dose and that there is limited additional value in reporting separate results for each of the separate doses and/or using separate scenarios.

5.3 Additional sensitivity analyses undertaken by the company in response to points for clarification

In response to the points for clarification, the company presented several additional scenario results. Table 39 summarises the scenarios, results and the company's conclusions.

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Table 39 Summary of additional scenarios presented in company response

Description of scenario	Results	Company conclusions
Inclusion of infliximab	A total of five sequences were dominated and were excluded from consideration. Infliximab, ixekizumab and brodalumab were both more costly and more effective than tildrakizumab and were associated with ICERs of £199,148, £367,658 and £6,693,147, respectively	Tildrakizumab is cost-effective versus each individual comparator sequence with a positive net monetary benefit value generated.
Use of 28 week effectiveness data for tildrakizumab sequence only	All sequences were dominated, with the exception of the tildrakizumab (sequence 1) and adalimumab (sequence 2) sequences. The ICER of tildrakizumab versus adalimumab was £22,689 per QALY.	The adalimumab sequence is the most cost-effective, based on a cost effectiveness threshold of £20,000. However, these results are marginal, such that a small increase in the cost-effectiveness threshold would make tildrakizumab the most cost-effective sequence
EQ-5D analysis based on UK value set	There were 3 non-dominated sequences. Of these, the least effective and lowest cost was the sequence starting with tildrakizumab (sequence 1). The ICER of the ixekizumab sequence (sequence 6) was reported to be £250,251 per QALY compared to the tildrakizumab sequence. The brodalumab sequence (sequence 7) was the most effective and most costly of the non-dominated sequences. The ICER of the brodalumab sequence versus the ixekizumab sequence was £4,326,207 per QALY.	Very similar to base case analysis. Tildrakizumab is cost-effective versus each individual comparator sequence with a positive net monetary benefit value generated.
Inclusion of non-responder costs	There were 3 non-dominated sequences. The least effective and lowest cost was the sequence starting with tildrakizumab (sequence 1). The ICER of the ixekizumab sequence (sequence 6) was reported to be £202,508 per QALY compared to the tildrakizumab sequence. The brodalumab sequence (sequence 7) was the most effective and most costly of the non-dominated sequences. The ICER of the brodalumab sequence versus the ixekizumab sequence was £4,541,894 per QALY.	Very similar to base case analysis. Tildrakizumab is cost-effective versus each individual comparator sequence with a positive net monetary benefit value generated.

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5.4 Conclusions of the cost effectiveness section

The company submission concludes that the tildrakizumab sequence was the most cost-effective sequence in their base case analysis. The company also concluded that this conclusion was broadly supported by the outputs for the sensitivity and scenario analyses.

The ERG highlights that the company's value proposition is that using tildrakizumab as the first biologic treatment in a sequence results in the lowest total cost of all the sequences compared. While using several other alternative treatments (secukinumab, ixekizumab, guselkumab and brodalumab) in the same position as tildrakizumab would lead to higher QALY outcomes (and higher costs). The company's results suggest that the additional cost incurred by the NHS to achieve these higher outcomes do not appear to represent value for money. Equally, using several other treatments (adalimumab, etanercept and ustekinumab) in the same position as tildrakizumab would lead to lower outcomes (and higher costs). The company's results suggest that a tildrakizumab sequence would dominate sequences which start with these other treatments.

The robustness of the company's value proposition for tildrakizumab is thus closely linked to the magnitude of the cost and QALY differences between the tildrakizumab sequence and the comparator sequences. One key uncertainty that the company is unable to address is the impact of the confidential PAS schemes for secukinumab, ixekizumab, guselkumab and brodalumab. The impact of including the confidential PAS schemes is presented in a separate confidential appendix to the ERG's report. The ERG also notes uncertainty regarding the comparison with adalimumab. The ERG notes that the differences in effects were small and the direction of the effect changed when a placebo adjustment was used in the NMA. In addition, the cost differences may be substantially altered when the biosimilar for adalimumab becomes available in the very near future.

The ERG's critique has also raised a number of issues and areas of uncertainty which might impact on the magnitude of the cost and QALY differences. A summary of the main issues and areas of uncertainty raised by the ERG is presented in Table 40. This table also considers the importance and potential magnitude of the impact of these issues and is used to prioritise the ERG's additional exploratory analyses presented in the following section

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Table 40 Summary of ERG's critique: key issues and areas of uncertainty

Section of ERG critique	Issue/area of uncertainty	Potential magnitude of impact on ICER	Part of ERG exploratory analyses
5.2.2 Model structure	Use of single PASI≥90 state and not separating into separate PASI 90-99 and PASI 100 states (as done in TA442 and TA511)	Negligible impact expected. Small differences reported in utilities between the PASI 90-99 and PASI 100 states. No differences in costs as identical costs assumed for all PASI ≥75 states.	No.
5.2.2 Model structure	Use of 14 common week cycle length results in a mismatch between the length of the induction period for the comparators and the time point recommended in previous NICE TAs.	Unclear. Impact will also vary depending on the dosing frequency and the extent of the mismatch.	Yes. Adjustments to cost of induction period proposed to match the time points recommended in previous NICE TAs.
5.2.2 Model structure	There exists clinical uncertainty surrounding the most appropriate response assessment period for tildrakizumab and also the cost-effectiveness of alternative stopping rules.	Unclear. However, the ERG considers that the cost-effectiveness of alternative stopping rules for tildrakizumab would be most appropriately informed by treating these as separate comparators	Yes. An additional sequence is considered assuming a 28 week stopping rule for tildrakizumab.
5.2.3 Population	The gender distribution assumed (50:50 male to female ratio) does not reflect the higher proportion of males within the reSURFACE trials (65%-75% male across the separate arms) [5]	Minor impact on incremental estimates expected. No meaningful bias given treatments not assumed to have any effect on mortality rate.	No.
5.2.4 Intervention and comparators	Company only presents comparisons for 8 sequences and only evaluates tildrakizumab in a 1st line position. Concerns have been expressed from previous ERG groups and NICE committees that modelling selective sequences (as opposed to all feasible sequences) could provide misleading estimates of cost-effectiveness	Unclear but critical in terms of interpreting the ICER results.	Yes. Alternative sequences and single treatment comparisons vs BSC explored to ensure sequence comparisons are logical and provide meaningful ICER results.
5.2.4 Intervention and comparators	Exclusion of infliximab as a relevant comparator. Despite limited use in clinical practice and in a more severe subgroup, the evidence from the infliximab trials may strengthen the network. For consistency with previous appraisals, infliximab should be included as a comparator.	Unclear but not expected to significantly alter conclusions.	Yes. Although main interest is in determining whether the additional infliximab trials alter the NMA inputs.
5.2.5 Perspective, time horizon and discounting	Lifetime horizon (approx. 58 years). Time horizon longer than other lifetime horizons used in previous appraisals, possibly due to 50:50 gender assumption. No sensitivity analyses or scenarios reported for shorter time horizons.	Minor impact on incremental estimates expected. No meaningful bias given treatments not assumed to have any effect on mortality rate.	No.

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5.2.6 Treatment effectiveness and extrapolation	The company's base case uses the Stage I network (12-16 week time point) and a random-effect model without placebo adjustment. The ERG's preferred network is the Stage 1 network including the infliximab trials. The best fitting statistical model for this network is the random-effect model without placebo adjustment.	Unclear. However, differences between some sequences are very small and hence the additional evidence and placebo adjustment may have a meaningful impact on the ICER results.	Yes. Impact of using the ERG's preferred network is assessed.
5.2.7 Discontinuation rates	Company base case applies the same constant discontinuation rate (18.7% per annum) to all treatments. Difficulties in generating robust estimates to inform treatment specific comparisons. Evidence from registries consistent in showing a lower risk of discontinuation for ustekinumab compared other anti-TNF treatments. Unclear whether this can be generalised to other IL-inhibitors (including tildrakizumab) using a class-effect assumption.	Unclear. However, the discontinuation rate was identified as an important driver in the company's DSA.	No. There is a lack of robust evidence for treatment specific differences.
5.2.8 Adverse events	Adverse events were excluded from the model.	Negligible impact expected. Low incidence of adverse events and no evidence that adverse events with tildrakizumab are higher than other treatments.	No.
5.2.9 Health related quality of life	Original company base case uses USA valuations for EQ-5D for USA patients in reSURFACE1. [5] Company provided revised analyses using UK valuations for all patients.	Unclear. Company scenario suggests negligible impact as results for most states were unaltered. However, higher utility value for PASI<50 in revised analysis may impact on overall model logic and possible implications for whether the ICER results are meaningful.	Yes. The impact of using UK values is assessed.
5.2.9 Health related quality of life	Company included adjustment to account for ageing. The proposed adjustment assumes a constant multiplicative relationship between age and PASI response. This was also implemented incorrectly. Further assumptions were also made to estimate an annual linear decrement.	Unclear. Company revised their model to address the programming error and this had a minor impact. However, the ERG considers that the proposed age-adjustment includes untested assumptions and does not appear to be necessary to generate unbiased ICER results.	Yes. The impact of excluding ageing is assessed.
5.2.9 Health related quality of life	ERG highlighted that the baseline EQ-5D estimate ([redacted]) is not used in the model. The minimum reference point for the utility estimates is [redacted] (PASI<50). Uncertainty concerning whether this is appropriate for BSC.	Unclear, although potentially important for BSC and hence the overall logic of the model and possible implications for whether the ICER results are meaningful.	Yes. An alternative scenario is evaluated using alternative EQ-5D estimate for BSC to explore the impact on the ICER results and overall model logic.

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5.2.10 Drug acquisition costs	Use of a common 14-week stopping rule creates bias in the induction costs for some comparators.	Unclear. Magnitude of any bias depends on dosing frequency for each treatment and the appropriate stopping rule.	Yes. A scenario is explored using the appropriate induction costs for all comparators, aligned with the time period stated in NICE guidance.
5.2.10 Drug acquisition costs	The ERG was unable to replicate the maintenance costs for some comparators.	Unclear. However, a difference of over £1,000 in the annual maintenance cost for guselkumab was identified using the ERG's calculation and the company's estimates.	Yes.
5.2.10 Administration costs	The company's base case does not include administration costs	Negligible impact expected.	No.
5.2.10 Non responder costs	Excluded from the company's base case. The estimate provided by the company in their response (£229) was not adjusted for the 14 week cycle. The ERG estimated the cost of non-response should be £801.50.	Potentially important as differences in the costs between some sequences are small.	Yes. An alternative scenario is evaluated using the ERG's preferred estimate.
5.2.10 BSC costs	The company's base case was based on estimates from NICE clinical guideline (CG153) and assumes a per-cycle (14 weeks) cost of £3,088 for BSC. The ERG considers that an alternative source (Fonia) is more consistent with recent NICE TAs. The equivalent per-cycle cost using Fonia is £1,422 for BSC.	Potentially important as differences in the costs between some sequences is small. Also potentially important implications for the overall logic of the model and whether the ICER results are meaningful.	Yes, An alternative scenario is evaluated using estimates from Fonia.
5.2.10 Adverse event costs	The costs of adverse events were not included in the company's base case. The ERG would have preferred to see a base case including adverse event costs.	Negligible impact expected.	No.
5.2.13 Probabilistic sensitivity analysis	The company's base case assigns independent distributions to the treatment effectiveness parameters and ignores the correlation between the efficacy inputs (PASI50, PASI75 and PASI90 response rates) and between individual treatments. The ERG does not consider that the uncertainty surrounding the effectiveness inputs has been appropriately characterised. In response to the point for clarification, the company updated the model such that the PASI outcomes were directly informed by the WinBUGS CODA with a sample of 3,000 iterations.	Unclear. Although the revised model addresses the ERG's concerns regarding the correlation between efficacy inputs and between individual treatments, the model runs each sequence individually and hence uses different random seeds for all other input parameters. Hence, the ERG does not consider that the PSA fully characterises decision uncertainty.	No.

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6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1.1 Model validation and face validity check

The company reported that the face validity of the model was assessed during the UK Advisory Board. The internal validity of the model was reported to have been assessed using a two-step process. The first step applied a cell-by-cell check of all model formulae to ensure they were correct and appropriately applied. In the second step, a model verification checklist was used, including a series of logical tests. The internal validation process was reported to have been undertaken by a health economist who was not directly involved in the conceptualisation and development of the model.

ERG commentary

The ERG undertook a review of the company's base-case, sensitivity and scenario analyses. All inputs were checked in the model against the estimates reported in the submission. The ERG also replicated the base-case, key sensitivity analyses and scenario analyses. The company results were also successfully replicated. The ERG also undertook a series of logical checks which confirmed that the model behaved logically. More detailed checks of the model coding identified a programing error in the calculation of age-adjusted utilities. This was raised with the company during the clarification stage and the company resubmitted a corrected model and revised EQ-5D data.

Table 41 summarises the results with the company's correction for the programming error and including the revised EQ-5D data. Although the company did not formally state that this was their revised base case, the ERG considers that this provides the closest representation of the company's base case while addressing the programming error and using the appropriate value set for EQ-5D. This table provides the reference point for the ERG's exploratory analyses.

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Table 41 Company corrected base case including revised EQ-5D estimates

Sequence				Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER (fully incremental)
1st	2nd	3rd	4th					
TIL	UST	SEC	BSC	[redacted]	[redacted]	NA	NA	-
ETN	UST	SEC	BSC	£236,523	[redacted]	-	-	Dominated
ADA	UST	SEC	BSC	£237,059	[redacted]	-	-	Dominated
UST	ADA	SEC	BSC	£237,822	[redacted]	-	-	Dominated
SEC	UST	ADA	BSC	£245,952	[redacted]	-	-	Ext. Dominated
IXE	UST	SEC	BSC	£265,026	[redacted]	[redacted]	[redacted]	£237,417
GUS	UST	SEC	BSC	£265,095	[redacted]	-	-	Dominated
BRO	UST	SEC	BSC	£267,202	[redacted]	[redacted]	[redacted]	£2,691,405

Key: ADA=adalimumab; BSC=best supportive care; BRO=brodalumab; ETN=etanercept; GUS=guselkumab; IXE=ixekizumab; SEC=secukinumab, UST=ustekinumab; NA=not applicable

The correction and revisions made by the company, did not lead to any meaningful differences compared to the company's original base case. In the fully incremental ICER comparison, the same three sequences were reported to be non-dominated (dominance and extended dominance). Of these, the least effective and lowest cost was the sequence starting with tildrakizumab (sequence 1). The ICER of the ixekizumab sequence (sequence 6) was reported to be £233,417 (vs £155,597 in the company's original base case) per QALY compared to the tildrakizumab sequence. The brodalumab sequence (sequence 7) was the most effective and most costly of the non-dominated sequences. The ICER of the brodalumab sequence versus the ixekizumab sequence was £2,691,405 (vs £2,817,613 in the company's original base case).

6.2 Overview

The ERG identified several key areas of uncertainty in the CS (see Table 40). The potential importance of these was considered and used to prioritise the ERG's exploratory analyses. Each of the priority issues is explored by the ERG in the following section. The findings from the ERG's exploratory analyses are considered and an alternative ERG base case is proposed at the end of this section.

As previously stated, the ERG considers that the most appropriate reference point for these exploratory analysis is the company's results correcting for the programming error and including the revised EQ-5D estimates. These results are summarised again in Table 42 (also previously reported in Section 5 - Table 41).

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Table 42 Company corrected base-case including revised EQ-5D estimates

Sequence				Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER (fully incremental)
1st	2nd	3rd	4th					
TIL	UST	SEC	BSC	[redacted]	[redacted]	NA	NA	-
ETN	UST	SEC	BSC	£236,523	[redacted]	-	-	Dominated
ADA	UST	SEC	BSC	£237,059	[redacted]	-	-	Dominated
UST	ADA	SEC	BSC	£237,822	[redacted]	-	-	Dominated
SEC	UST	ADA	BSC	£245,952	[redacted]	-	-	Ext. Dominated
IXE	UST	SEC	BSC	£265,026	[redacted]	[redacted]	[redacted]	£237,417
GUS	UST	SEC	BSC	£265,095	[redacted]	-	-	Dominated
BRO	UST	SEC	BSC	£267,202	[redacted]	[redacted]	[redacted]	£2,691,405

Key: ADA=adalimumab; BSC=best supportive care; BRO=brodalumab; ETN=etanercept; GUS=guselkumab; IXE=ixekizumab; SEC=secukinumab, UST=ustekinumab; NA=not applicable

The results of all the subsequent ERG analyses build on the results presented in Table 42.

6.3 Issue 1: Sequencing

The ERG was concerned that the company only presented comparisons for eight sequences and only evaluated tildrakizumab in a 1st line position. The ERG also noted concerns cited in previous NICE TAs that modelling selective sequences (as opposed to all feasible sequences) could provide misleading cost-effectiveness estimates.

The 1st exploratory analysis addressed the concern that including non-cost-effective comparators could generate misleading ICER results for the sequence comparisons. Table 43 shows the results of each individual treatment compared to BSC alone. This exploratory analysis is not intended to suggest that BSC is an appropriate comparator but rather to understand the model logic and to address concerns regarding the interpretation of the sequence ICER results.

The results show that four of the treatments appear to dominate BSC (etanercept, tildrakizumab, adalimumab and ustekinumab) and four treatments have ICER's which exceed conventional NICE thresholds (£20,000 to £30,000). Comparing the fully incremental ICERs, etanercept is the least costly and least effective treatment. The next most effective treatment is tildrakizumab with an ICER of £922 per QALY compared to etanercept. Of the remaining non-dominated treatments, both ixekizumab and brodalumab have ICER's compared to tildrakizumab which exceed conventional NICE thresholds.

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Table 43 Single treatment sequences vs BSC

Sequence				Mean cost	Mean QALY	Incr. cost	Incr. QALY	ICER (fully incremental)	ICER vs BSC (pairwise)
1st	2nd	3rd	4th						
ETN	BSC	BSC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	Dominates
TIL	BSC	BSC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£922	Dominates
ADA	BSC	BSC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominates
UST	BSC	BSC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated	Dominates
BSC	BSC	BSC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
SEC	BSC	BSC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated	£56,905
GUS	BSC	BSC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£61,268
IXE	BSC	BSC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£199,568	£56,429
BRO	BSC	BSC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£2,691,405	£61,595

Although Table 43 lends support to the company's conclusions based on their sequence comparison, the inclusion of treatments which appear less cost-effective than BSC can result in challenges in terms of interpreting ICERs based on partial sequence comparisons.

The ERG illustrates the problems with a simple example reported in Table 44. In this example, the ERG includes four select sequences which explore different positions for tildrakizumab. The reference sequence is a sequence without tildrakizumab; specifically: adalimumab>ustekinumab>secukinumab>BSC. The ERG highlights that two of the sequences are ruled out on the grounds of dominance and extended dominance. The lowest cost (non-dominated sequence) is the sequence where tildrakizumab is used 3rd in the sequence. Although using tildrakizumab as a 1st line treatment results in the highest QALYs, the ICER of this sequence versus using tildrakizumab as a 3rd line treatment exceed conventional NICE thresholds (£20,000 to £30,000).

The intention of this analysis is not to suggest that tildrakizumab is more cost-effective as a 3rd line treatment but rather to show the problems of including non-cost-effective treatments (e.g. secukinumab, see table Table 43) and presenting partial sequence comparisons. The reason that tildrakizumab appears most cost-effective as a 3rd line treatment is primarily because this is the only

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sequence where secukinumab is displaced. Since secukinumab was shown in the previous table to be less cost-effective than BSC, the sequence which results in secukinumab being displaced confers the greatest value. The fact that this is the sequence where tildrakizumab is positioned 3rd is simply an artefact of the partial set of sequences being compared.

Table 44 Example illustrating problems of modelling select sequences

Sequence				Mean cost	Mean QALY	Incremental cost	Incremental QALY	ICER
1st	2nd	3rd	4th					
ADA	UST	TIL	BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
ADA	TIL	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
TIL	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£189,614
ADA	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

The results of this simple example show the difficulties in generating meaningful ICER results from partial sequence comparisons, particularly when non-cost-effective comparators are included within a sequence. The ERG concludes that presenting fully incremental ICER results in this situation for partial sequences can be highly misleading. As a result, the ERG urges significant caution when considering fully incremental ICERs estimated using partial sequence analyses.

Given these problems, the remainder of the ERG's exploratory analyses focus on the comparisons of single treatments versus BSC alone. These comparisons avoid the problems noted above and allow more meaningful assessments of the remaining areas of uncertainty identified in the ERG's critique. However, having better understood the implications of these uncertainties, the ERG return to the same sequences considered by the company in their revised base case and considers the implications of their exploratory findings.

As outlined by the ERG for TA511 (brodalumab), a further advantage of using the net-benefit framework is that it can simplify the fully incremental comparisons and also the sequential treatment comparisons, due to two key assumptions made in the company base-case; specifically:

(i) the effectiveness of each treatment is independent of its position in any sequence. That is, the PASI response rates for each treatment are the same regardless of whether a treatment is positioned first, second or last in a sequence, prior to receipt of BSC;

(ii) the withdrawal rate of each treatment over the maintenance period is the same and constant over time.

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Employing these assumptions, the ERG for TA511 proposed that the incremental net-benefits of each individual treatment versus BSC alone (and associated rankings) could be used as a basis for establishing:

(i) whether a specific treatment has the potential to be cost-effective within a sequence (i.e. whether a particular treatment appears cost-effective compared to BSC);

(ii) the most efficient positioning of a treatment in a sequence (i.e. whether a particular treatment appears more or less cost-effective than another active comparator).

Treatments with a pairwise ICER versus BSC alone that are lower than the ICER threshold (£20,000 - £30,000) also have a positive NMB. However, the additional advantage of the NMB statistic is that the rankings of treatments (from highest NMB to lowest NMB) also indicate which treatment is most cost-effective and avoids the complexities of estimating fully incremental ICER estimates. That is, the most cost-effective single treatment is the one which has the highest (positive) NMB versus BSC alone.

Although these comparisons are most relevant to a decision where individuals are only permitted to receive one line of therapy prior to BSC, the framework and results can be generalised to sequential considerations. That is, any treatment which has a NMB<0 (compared to BSC alone) would never form part of an efficient (i.e. cost-effective) sequence. Any treatment which has a NMB>0 compared to BSC alone has the potential to be cost-effective within a sequence. The subsequent inclusion and positioning of those treatments with a positive NMB would then be determined by the net benefit ranking and other considerations (e.g. external constraints on the maximum length of any sequence). That is, the most efficient sequence would start with the top ranked treatment (i.e. highest NMB) and proceed to the next highest ranked treatment and on down the list.

A similar approach is used in the ERG's exploratory analysis section below.

6.4 Issue 2: NMA and inclusion of relevant comparators (infliximab)

The company's base case uses the Stage I network (12-16 week time point) and a random-effect model without placebo adjustment. The ERG's preferred NMA is the Stage I NMA including the infliximab trials. The best fitting statistical model for this network is the random-effect model without placebo adjustment.

Table 45 summarises the results using the ERG's preferred NMA, including the additional infliximab trials and also including infliximab as an additional comparator. The results indicate that the following treatments do not appear to be cost-effective at either a £20,000 or £30,000 per QALY threshold:

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brodalumab; guselkumab; infliximab; ixekizumab; and secukinumab. The ERG notes that these results do not include the confidential PAS schemes for brodalumab, guselkumab, ixekizumab and secukinumab (reported separately in the ERG's confidential appendix). All of the remaining treatments are more cost-effective than BSC alone and have the potential to be in an efficient sequence depending on whether there are constraints on the overall length of a sequence.

The CS restricts the overall length of any sequence to three active lines of treatment prior to BSC alone. Constraining the sequence options to three active lines of treatment, the ordering and positioning of treatments can be informed by the rankings:

- At a £20,000 and £30,000 threshold, the optimal treatment based on NMB (vs BSC alone) is: *tildrakizumab (100mg)*.

Although the random effect model without placebo adjustment appeared to fit better than a model with placebo adjustment (DIC measure = 3082 vs 3088), the ERG explored the robustness of the conclusions to including a placebo adjustment.

Table 46 summarises the cost-effectiveness results (and incremental net-benefit and rankings) for the same evidence network but using the random-effects model with a placebo adjustment.

- At a £20,000 threshold, the optimal treatment based on NMB (vs BSC alone) is: *tildrakizumab (100mg)*.
- At a £30,000 threshold, the optimal treatment based on NMB (vs BSC alone) changes to: *adalimumab*.

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Table 45 Revised NMA including infliximab (RE – not placebo adjusted): Pairwise ICERs vs BSC and NMB rankings

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
Etanercept	£225,173	[redacted]	[redacted]	[redacted]	Dominates	£8,791	4	£10,043	4
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	£11,445	**1**	£14,087	**1**
Adalimumab	£226,209	[redacted]	[redacted]	[redacted]	Dominates	£10,444	**2**	£13,039	**2**
Ustekinumab	£228,200	[redacted]	[redacted]	[redacted]	Dominates	£8,819	**3**	£11,597	**3**
BSC	£231,461	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Infliximab	£243,170	[redacted]	[redacted]	[redacted]	£30,949	-£4,142	5	-£359	5
Secukinumab	£253,299	[redacted]	[redacted]	[redacted]	£56,496	-£14,107	6	-£10,241	6
Guselkumab	£254,778	[redacted]	[redacted]	[redacted]	£61,018	-£15,674	8	-£11,853	8
Ixekizumab	£254,783	[redacted]	[redacted]	[redacted]	£55,980	-£14,989	7	-£10,823	7
Brodalumab	£257,018	[redacted]	[redacted]	[redacted]	£61,346	-£17,225	9	-£13,059	9

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Table 46 Revised NMA including infliximab (RE – placebo adjusted): Pairwise ICERs vs BSC and NMB rankings

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	£11,885	**1**	£14,748	**2**
Etanercept	£225,579	[redacted]	[redacted]	[redacted]	Dominates	£8,362	4	£9,601	4
Adalimumab	£225,864	[redacted]	[redacted]	[redacted]	Dominates	£11,748	**2**	£14,823	**1**
Ustekinumab	£228,095	[redacted]	[redacted]	[redacted]	Dominates	£9,538	**3**	£12,624	**3**
BSC	£231,461	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Infliximab	£242,781	[redacted]	[redacted]	[redacted]	£30,753	-£3,958	5	-£277	5
Secukinumab	£252,772	[redacted]	[redacted]	[redacted]	£55,136	-£13,580	6	-£9,715	6
Ixekizumab	£254,144	[redacted]	[redacted]	[redacted]	£55,076	-£14,446	7	-£10,327	7
Guselkumab	£255,335	[redacted]	[redacted]	[redacted]	£55,996	-£15,347	8	-£11,083	8
Brodalumab	£257,185	[redacted]	[redacted]	[redacted]	£57,452	-£16,769	9	-£12,291	9

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Although the same treatments are consistently ranked in the top three NMB rankings, the ordering of these treatments alters depending on whether an adjustment is made for placebo response and the cost-effectiveness threshold. The change in ranking is most evident been tildrakizumab (100mg) and adalimumab. The rankings of these treatments differs depending on whether an adjustment is made (or not) for differences in the placebo response. This indicates that the magnitude of difference in the QALY estimates between these treatments is small and sensitive to adjustments due to differences in the placebo rates across the trials.

All of the analyses from this point onwards use the ERG's preferred NMA without placebo adjustment.

6.5 Issue 3: Induction period for tildrakizumab (14 weeks or 28 weeks)

The ERG highlighted that there exists clinical uncertainty surrounding the most appropriate response assessment period for tildrakizumab and also the cost-effectiveness of alternative stopping rules. Although the company provided a scenario analysis assuming a 28 week stopping rule for tildrakizumab, the ERG noted concerns that this analysis also assumed a 28 week stopping rule for other comparators. The ERG also concluded that the cost-effectiveness of alternative stopping rules for tildrakizumab would be most appropriately informed by having different stopping rules for tildrakizumab as separate comparators and not including a 28 week stopping rule for the other treatments.

Table 47 summarises the cost-effectiveness results (and incremental net-benefit and rankings) including alternative stopping rules for tildrakizumab.

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Table 47 Alternative induction periods for tildrakizumab (14 weeks and 28 weeks): Pairwise ICERs vs BSC and NMB rankings

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
Etanercept	£225,173	[redacted]	[redacted]	[redacted]	Dominates	£8,791	5	£10,043	5
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	£11,445	**2**	£14,087	**2**
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	£12,592	**1**	£15,962	**1**
Adalimumab	£226,209	[redacted]	[redacted]	[redacted]	Dominates	£10,444	**3**	£13,039	**3**
Ustekinumab	£228,200	[redacted]	[redacted]	[redacted]	Dominates	£8,819	4	£11,597	4
BSC	£231,461	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Infliximab	£243,170	[redacted]	[redacted]	[redacted]	£30,949	-£4,142	6	-£359	6
Secukinumab	£253,299	[redacted]	[redacted]	[redacted]	£56,496	-£14,107	7	-£10,241	7
Guselkumab	£254,778	[redacted]	[redacted]	[redacted]	£61,018	-£15,674	9	-£11,853	9
Ixekizumab	£254,783	[redacted]	[redacted]	[redacted]	£55,980	-£14,989	8	-£10,823	8
Brodalumab	£257,018	[redacted]	[redacted]	[redacted]	£61,346	-£17,225	10	-£13,059	10

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- At a £20,000 and £30,000 threshold, the optimal treatment based on NMB (vs BSC alone) is: tildrakizumab 100mg (28 weeks).

The ERG's exploratory analysis suggests that a 28 week stopping rule for tildrakizumab (28 weeks) appears more cost-effective than a 14 week period. This is due to the better efficacy for tildrakizumab from the Stage III (24/28 weeks) NMA and the longer time until patients enter BSC treatment. The ERG notes that the Stage III (24/28 weeks) NMA is less robust and may be less reliable than the Stage I (12/16 weeks) NMA as it includes extrapolated placebo data and some uncontrolled treatment data.

All of the exploratory analyses from this point onwards include a 28 week stopping for tildrakizumab as an additional comparator.

6.6 Issue 4: Induction periods for comparators and costs (induction and maintenance)

In Section 5.2.10, the ERG highlighted that the assumption of a common 14-week stopping rule creates bias in the induction costs for some comparators. The ERG was also unable to replicate the maintenance costs for some comparators. Table 48 summarises the cost-effectiveness results (and incremental net-benefit and rankings) using the ERG's preferred induction and maintenance cost assumptions.

At a £20,000 and £30,000 threshold, the optimal treatment based on NMB (vs BSC alone) was the same as when the company's induction and maintenance cost assumptions were used: *tildrakizumab 100mg (28 weeks)*. Hence, although the ERG identified a potential bias in the company's estimates, the ERG's revisions resulted in no meaningful difference to the conclusions.

All of the ERG's exploratory analyses from this point forward continue to build on the previous analyses. That is, they are based on the ERG's preferred network (including infliximab as an additional comparator), they include an additional strategy reflecting a 28 week stopping rule for tildrakizumab and they include the ERG's preferred assumptions for the costs of induction and maintenance.

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Table 48 ERG's preferred induction and maintenance costs: Pairwise ICERs vs BSC and NMB rankings

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
Etanercept	£224,692	[redacted]	[redacted]	[redacted]	Dominates	£9,272	4	£10,524	5
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	£11,445	**2**	£14,087	**2**
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	£12,592	**1**	£15,962	**1**
Adalimumab	£226,736	[redacted]	[redacted]	[redacted]	Dominates	£9,917	**3**	£12,513	**3**
Ustekinumab	£228,096	[redacted]	[redacted]	[redacted]	Dominates	£8,923	5	£11,702	4
BSC	£231,461	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Infliximab	£242,861	[redacted]	[redacted]	[redacted]	£30,134	-£3,834	6	-£51	6
Guselkumab	£250,674	[redacted]	[redacted]	[redacted]	£50,277	-£11,570	7	-£7,748	7
Secukinumab	£251,628	[redacted]	[redacted]	[redacted]	£52,173	-£12,436	8	-£8,570	8
Ixekizumab	£253,101	[redacted]	[redacted]	[redacted]	£51,943	-£13,308	9	-£9,141	9
Brodalumab	£256,062	[redacted]	[redacted]	[redacted]	£59,050	-£16,268	10	-£12,102	10

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6.7 Issue 5: Cost of BSC

As highlighted in Section 5.2.10, the ERG considers that the costs of BSC based on an alternative source (Fonia) is more appropriate (and consistent with recent NICE TAs) compared to the company's base case approach based on estimates from NICE clinical guideline (CG153). The ERG's preferred source imply a per-cycle (14 weeks) cost of £1,422 for BSC. This is markedly lower than the estimate of £3,088 used in the company's base case.

Table 49 summarises the cost-effectiveness results (and incremental net-benefit and rankings) using the ERG's preferred estimate for the cost of BSC. It is evident from these results that using the alternative source leads to significant differences in results, with important implications for the interpretation of the cost-effectiveness results.

At a £20,000 and £30,000 per QALY threshold:

- None of the treatments are cost-effective compared to BSC alone.
- The optimal treatment based on NMB (vs BSC alone) is: *etanercept*..

The findings from this analysis reinforce the ERG's concerns regarding the interpretation of ICER's based on the company's sequence approach. As none of the treatments are cost-effective compared to BSC, none of the treatments would appear in the most efficient sequence. Indeed, the optimal sequence would be to use BSC alone.

Working on the assumption that BSC alone is not considered a relevant comparator, the rankings of NMB across the various treatment imply a different ordering from previous analyses. However, it should also be understood that the rankings are based on negative net monetary benefit estimates. In this situation, the cheapest and least effective treatment (etanercept) has the highest ranking. However, this is simply because a higher proportion of patients will not respond and hence will proceed to BSC more quickly. The implications of this finding need to be carefully considered and further reinforce the ERG's concerns regarding the misleading nature of fully incremental ICERs based on partial sequence comparisons.

All of the ERG's exploratory analyses from this point forward continue to build on the previous analyses and include the ERG's preferred source for the cost of BSC.

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Table 49 ERG's preferred source for the costs of BSC: Pairwise ICERs vs BSC and NMB rankings

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
BSC	£106,598	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Etanercept	£114,562	[redacted]	[redacted]	[redacted]	£63,640	-£5,461	**1**	-£4,210	**1**
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£56,323	-£9,597	**2**	-£6,955	**2**
Adalimumab	£122,728	[redacted]	[redacted]	[redacted]	£62,140	-£10,938	**3**	-£8,343	**3**
Ustekinumab	£124,830	[redacted]	[redacted]	[redacted]	£65,615	-£12,675	5	-£9,896	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£55,087	-£11,825	4	-£8,455	4
Infliximab	£143,677	[redacted]	[redacted]	[redacted]	£98,013	-£29,513	6	-£25,730	6
Guselkumab	£151,674	[redacted]	[redacted]	[redacted]	£117,961	-£37,434	7	-£33,613	7
Secukinumab	£152,814	[redacted]	[redacted]	[redacted]	£119,568	-£38,486	8	-£34,620	8
Ixekizumab	£155,400	[redacted]	[redacted]	[redacted]	£117,144	-£40,471	9	-£36,304	9
Brodalumab	£158,361	[redacted]	[redacted]	[redacted]	£124,251	-£43,431	10	-£39,265	10

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6.8 Issue 6: HRQoL assumptions

In Section 5.2.9, the ERG highlighted the proposed age-adjustment to utility inputs included untested assumptions (e.g. multiplicative relationship with age). The ERG also concluded that age-adjustment was not necessary to generate unbiased ICER results.

The ERG also notes that the baseline EQ-5D estimate ([redacted]) is not used in the model. The minimum reference point for the utility estimates is [redacted] (PASI<50). The ERG notes that there were significant uncertainties concerning whether these estimates could be generalised to people receiving BSC alone.

Given the ERG's concerns regarding the implementation and assumptions of age-adjustment, the ERG's preferred approach was to use the absolute utility values for the PASI states without age-adjustment. Table 50 summarises the ERG's results removing the age-adjustment from the utility inputs.

The ERG also explored the impact of alternative assumptions concerning the HRQoL of patients receiving BSC alone. Specifically, the ERG explored a scenario where patients receiving only BSC received the baseline EQ-5D estimate. Table 50 summarises the ERG's results removing the age-adjustment from the utility inputs and using the baseline EQ-5D utility value for patients receiving BSC alone.

When the adjustment for ageing was excluded from the model, there was no material change in the conclusions. This supported the ERG's view that the excluding ageing was not necessary to generate unbiased ICER results. Furthermore, the ERG notes that the use of absolute utilities is consistent with all previous NICE TAs. The results showed that:

At £20,000 and £30,000 per QALY threshold:

- None of the treatments are cost-effective compared to BSC alone.
- The optimal treatment based on NMB (vs BSC alone) is: *etanercept.*

When the adjustment for ageing was excluded from the model and it was also assumed that patients receiving BSC alone reverted back to their baseline EQ-5D value, there was a material change in the conclusions. Table 51 shows the impact of excluding ageing adjustment and applying baseline utilities to the patients receiving BSC.

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Table 50 Impact of excluding ageing: Pairwise ICERs vs BSC and NMB rankings

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
BSC	£106,598	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Etanercept	£114,562	[redacted]	[redacted]	[redacted]	£64,912	-£5,510	**1**	-£4,283	**1**
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£56,031	-£9,569	**2**	-£6,913	**2**
Adalimumab	£122,728	[redacted]	[redacted]	[redacted]	£61,842	-£10,913	**3**	-£8,305	**3**
Ustekinumab	£124,830	[redacted]	[redacted]	[redacted]	£65,203	-£12,640	5	-£9,843	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£54,531	-£11,757	4	-£8,352	4
Infliximab	£143,677	[redacted]	[redacted]	[redacted]	£96,848	-£29,422	6	-£25,593	6
Guselkumab	£151,674	[redacted]	[redacted]	[redacted]	£116,542	-£37,341	7	-£33,473	7
Secukinumab	£152,814	[redacted]	[redacted]	[redacted]	£118,108	-£38,390	8	-£34,477	8
Ixekizumab	£155,400	[redacted]	[redacted]	[redacted]	£115,585	-£40,358	9	-£36,136	9
Brodalumab	£158,361	[redacted]	[redacted]	[redacted]	£122,597	-£43,319	10	-£39,097	10

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Table 51 Impact of excluding ageing and assuming patients receiving BSC revert to baseline EQ-5D utility: Pairwise ICERs vs BSC and NMB rankings

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
BSC	£106,598	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Etanercept	£114,562	[redacted]	[redacted]	[redacted]	£14,162	£3,283	**1**	£8,907	4
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£17,411	£2,212	**2**	£10,759	**2**
Adalimumab	£122,728	[redacted]	[redacted]	[redacted]	£19,078	£780	4	£9,234	**3**
Ustekinumab	£124,830	[redacted]	[redacted]	[redacted]	£20,675	-£596	5	£8,223	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£18,444	£1,566	**3**	£11,632	**1**
Infliximab	£143,677	[redacted]	[redacted]	[redacted]	£34,313	-£15,467	6	-£4,661	6
Guselkumab	£151,674	[redacted]	[redacted]	[redacted]	£41,394	-£23,297	7	-£12,407	7
Secukinumab	£152,814	[redacted]	[redacted]	[redacted]	£42,099	-£24,260	8	-£13,282	8
Ixekizumab	£155,400	[redacted]	[redacted]	[redacted]	£42,269	-£25,711	9	-£14,165	9
Brodalumab	£158,361	[redacted]	[redacted]	[redacted]	£44,833	-£28,672	10	-£17,126	10

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At £20,000 per QALY threshold:

- The following treatments are now cost-effective compared to BSC alone: *adalimumab, etanercept, tildrakizumab 100mg (14 weeks), tildrakizumab 100mg (28 weeks).*
- The optimal treatment based on NMB (vs BSC alone) is: *etanercept.*

At £30,000 per QALY threshold:

- The following treatments are now cost-effective compared to BSC alone: *adalimumab, etanercept, tildrakizumab 100mg (14 weeks), tildrakizumab 100mg (28 weeks*) and *ustekinumab.*
- The optimal treatment based on NMB (vs BSC alone) is: tildrakizumab 100mg (28 weeks).

As is evident from these findings, the different assumptions used for the utility of patients receiving BSC alone have important implications, both in terms of the cost-effectiveness of each treatment when compared with BSC alone but also in terms of the rankings and implied ordering of specific treatments in an efficient sequence.

The ERG's exploratory analyses from this point forward continue to build on the previous analyses and exclude the impact of ageing. The assumption that patients receiving BSC revert back to baseline utility is not included in the remainder of the ERG's exploratory analysis. However, the ERG highlights that this assumption appears to be one of the two main cost-effectiveness drivers (cost of BSC and HRQoL of people receiving BSC). Hence, the ERG return to this issue when presenting their alternative base-case results.

6.9 Cost of non-response

In Section 5.2.10, the ERG noted that the costs of non-response were excluded from the company's base case. Although the company subsequently provided a scenario including a cost for non-response (£229), the ERG identified that this estimated had not been appropriately adjusted for the 14 week cycle length. The ERG estimated the cost of non-response should be £801.50.

Table 52 summarises the results using the ERG's preferred estimate for the cost of non-response.

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Table 52 ERG's preferred estimates for the cost of non-response: Pairwise ICERs vs BSC and NMB rankings

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
BSC	£109,299	[redacted]	[redacted]	[redacted]	NA	NA	**1**	NA	**1**
Etanercept	£116,928	[redacted]	[redacted]	[redacted]	£62,183	-£5,176	**2**	-£3,949	**2**
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£53,786	-£8,973	**3**	-£6,317	**3**
Adalimumab	£124,840	[redacted]	[redacted]	[redacted]	£59,586	-£10,325	4	-£7,717	4
Ustekinumab	£126,912	[redacted]	[redacted]	[redacted]	£62,989	-£12,021	6	-£9,224	6
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£53,265	-£11,325	5	-£7,921	5
Infliximab	£145,590	[redacted]	[redacted]	[redacted]	£94,789	-£28,634	7	-£24,805	7
Guselkumab	£153,580	[redacted]	[redacted]	[redacted]	£114,484	-£36,545	8	-£32,677	8
Secukinumab	£154,711	[redacted]	[redacted]	[redacted]	£116,054	-£37,586	9	-£33,673	9
Ixekizumab	£157,252	[redacted]	[redacted]	[redacted]	£113,572	-£39,508	10	-£35,286	10
Brodalumab	£160,212	[redacted]	[redacted]	[redacted]	£120,585	-£42,469	11	-£38,247	11

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When the ERG's preferred estimate for the cost of non-response was included, there was no material change in the conclusions. This suggests that the cost of non-response does not appear to be an important driver of cost-effectiveness.

6.10 ERG alternative base case

An alternative ERG alternative base case is presented based on the findings and implications of the ERG's exploratory analysis. Table 53 summarises the key issues identified by the ERG and the assumptions employed in the company's base case and the ERG's alternative base case.

Table 53 Comparison of approaches and assumptions in company base case and ERG alternative base case

No.	1ssue	Company base case	ERG alternative base case
1.	Sequencing	Comparisons for 8 sequences and only evaluates tildrakizumab in a 1st line position.	Comparisons of individual treatments vs BSC alone (pairwise ICER and NMB). NMB rankings and implied order of treatments based on efficiency. Consideration of any implications for fully incremental ICERs for the 8 sequences.
2	NMA and inclusion of relevant comparators (infliximab)	Random-effect without placebo adjustment from network without infliximab trials. Infliximab excluded as a relevant comparator.	Random-effect without placebo adjustment from network with infliximab trials. Infliximab included as a relevant comparator.
3	Induction period for tildrakizumab (14 weeks or 28 weeks)	14 week induction period for tildrakizumab. Separate scenario for 28 week induction period for tildrakizumab.	Alternative induction periods for tildrakizumab included as separate comparators.
4	Induction period for comparators and costs (induction and maintenance)	Costs based on 14 week induction period for all comparators. Dose adjustments made to estimate maintenance costs for a 14 week cycle.	Induction costs based on recommended stopping rules applied in previous NICE TAs. Annual treatment costs estimated and converted to 14 week cycle.
5	Cost of BSC	NICE GC153	Fonia et al. [44]
6	HRQoL assumptions	Including age adjustment. HRQoL of BSC based on placebo PASI responses in trial and PASI utilities for each PASI response state.	Excluding age adjustment HRQoL of BSC based on placebo PASI responses in trial and PASI utilities for each PASI response state.

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			Additional scenario assuming utility of BSC = baseline EQ-5D value.
7	Cost of non-responders	Not included.	Additional cost of £801.50

Although the ERG's alternative base case encompasses alternative approaches and assumptions for seven key areas, the ERG considers that the main uncertainties and committee's considerations should be focused on 3 specific areas:

1) <u>The different approaches to dealing with sequences</u>

A key difference between the approaches concerns the sequence comparisons. The company's base case presents fully incremental comparisons of 8 sequences and only considers tildrakizumab in a front line position. However, the company does not explicitly address the potential problems of evaluating partial sequences and the possible inclusion of non-cost-effective comparators.

The ERG's alternative base case looks more carefully at the potential problems by first considering the cost-effective of each individual treatment versus BSC alone. These results can be used to identify the possible inclusion of non-cost-effective comparators. The NMB rankings based on these comparisons can also be used to address the problems of evaluating partial sequences. That is, they can be used to inform whether a particular treatment has the potential to be cost-effective within a sequence (i.e. whether it appears cost-effective compared to BSC alone) and most efficient positioning of a treatment in a sequence (i.e. whether it appears more or less cost-effective than another active comparator).

The ERG considers that these comparisons can be used to inform decision making and also can provide important additional insights which help to interpret the fully incremental ICERs based on partial sequence comparisons.

2) <u>The different assumptions for the cost of BSC</u>

While the ERG considers that the estimates reported by Fonia et al (2010) appear more appropriate than the company's base case inputs, the committee also needs to be aware that this also results in none of the treatments appearing more cost-effective than BSC alone. [44] The implication of this is that the most efficient (i.e. cost-effective sequence) would be a sequence without any biologic treatment.

The ERG is not trying to suggest that BSC alone is the relevant option, but rather to highlight the challenges of assessing the cost-effectiveness of partial sequence comparisons in this situation. As

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was evident from the ERG's exploratory analysis, the most cost effective sequence of three biologic treatments in this situation would be a sequence which combines the cheapest and least effective treatments. However, this is simply because this sequence would increase the probability and hence speed that patients eventually end up receiving BSC alone. The quicker people end up at the last treatment in the sequence (i.e. BSC alone) the lower the opportunity cost for the NHS (i.e. the displacement of higher value activities elsewhere to fund the additional cost of more effective but higher cost treatments).

The implications of this finding need to be carefully considered when assessing the fully incremental ICER comparisons and further reinforce the ERG's concerns regarding the potential for these to provide misleading estimates when based on partial sequence comparisons.

3) Uncertainties surrounding the HRQoL of people receiving BSC alone

The final area is the HRQoL of people who receive BSC alone. The ERG's critique highlighted that the baseline EQ-5D estimate ( ) is not used in the model. Instead, the minimum utility estimate applied in the model is (PASI<50). The reason for this difference and the generalisability of the PASI utilities for each response category to people who receive BSC alone is unclear. However, it is also evident that this assumption is a critical driver of the cost-effectiveness results. The ERG's exploratory analyses show that when an alternative assumption is made, namely that the utility of people who receive BSC alone reverts back to the baseline utility, the implications for cost-effectiveness are completely different. That is, treatments which were previously less cost-effective than BSC alone now become more cost-effective.

Again, the implications of this finding need to be carefully considered when assessing the fully incremental ICER comparisons. Given the importance and logical implications of this specific area of uncertainty, the ERG presents their alternative base case using two alternative assumptions regarding the HRQoL of people who receive BSC. One approach uses the same assumption as used by the company, such that the utility values for BSC are determined by the distribution of placebo responses across the four PASI response states (PASI <50 [utility value =], PASI 50-74 [utility value =], PASI 75-89 [utility value =], PASI ≥90 [utility value =]) informed from the NMA. The second approach assumes that the utility value of people receiving BSC alone is the same as the baseline utility ( ).

Table 54 and Table 55 report the results from the ERG's alternative base case using these alternative approaches.

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Table 54 ERG alternative base case: Pairwise ICERs vs BSC and NMB rankings

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
BSC	£106,598	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Etanercept	£114,562	[redacted]	[redacted]	[redacted]	£64,912	-£5,510	**1**	-£4,283	**1**
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£56,031	-£9,569	**2**	-£6,913	**2**
Adalimumab	£122,728	[redacted]	[redacted]	[redacted]	£61,842	-£10,913	**3**	-£8,305	**3**
Ustekinumab	£124,830	[redacted]	[redacted]	[redacted]	£65,203	-£12,640	5	-£9,843	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£54,531	-£11,757	4	-£8,352	4
Infliximab	£143,677	[redacted]	[redacted]	[redacted]	£96,848	-£29,422	6	-£25,593	6
Guselkumab	£151,674	[redacted]	[redacted]	[redacted]	£116,542	-£37,341	7	-£33,473	7
Secukinumab	£152,814	[redacted]	[redacted]	[redacted]	£118,108	-£38,390	8	-£34,477	8
Ixekizumab	£155,400	[redacted]	[redacted]	[redacted]	£115,585	-£40,358	9	-£36,136	9
Brodalumab	£158,361	[redacted]	[redacted]	[redacted]	£122,597	-£43,319	10	-£39,097	10

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Table 55 ERG alternative base case (including additional assumption that utility of BSC = baseline utility): Pairwise ICERs vs BSC and NMB rankings

	ICER estimates					Net Monetary Benefit estimates			
Drug (1 line only)	**Total cost**	**Total QALYs**	**Incremental cost vs BSC**	**Incremental QALYs vs BSC**	**pairwise ICER vs BSC**	**INB vs BSC @20k**	**Rank @20k**	**INB vs BSC @30k**	**Rank @30k**
BSC	£106,598	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Etanercept	£114,562	[redacted]	[redacted]	[redacted]	£14,162	£3,283	**1**	£8,907	4
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£17,411	£2,212	**2**	£10,759	**2**
Adalimumab	£122,728	[redacted]	[redacted]	[redacted]	£19,078	£780	4	£9,234	**3**
Ustekinumab	£124,830	[redacted]	[redacted]	[redacted]	£20,675	-£596	5	£8,223	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£18,444	£1,566	**3**	£11,632	**1**
Infliximab	£143,677	[redacted]	[redacted]	[redacted]	£34,313	-£15,467	6	-£4,661	6
Guselkumab	£151,674	[redacted]	[redacted]	[redacted]	£41,394	-£23,297	7	-£12,407	7
Secukinumab	£152,814	[redacted]	[redacted]	[redacted]	£42,099	-£24,260	8	-£13,282	8
Ixekizumab	£155,400	[redacted]	[redacted]	[redacted]	£42,269	-£25,711	9	-£14,165	9
Brodalumab	£158,361	[redacted]	[redacted]	[redacted]	£44,833	-£28,672	10	-£17,126	10

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The results of Table 54 show:

At £20,000 and £30,000 per QALY threshold:

The following treatments are cost-effective compared to BSC alone: *None*

The optimal treatment based on NMB (vs BSC alone) is: *etanercept.*

The results of Table 55 (assuming utility for BSC = baseline) show:

At a £20,000 per QALY threshold:

The following treatments are cost-effective compared to BSC alone: *adalimumab, etanercept, tildrakizumab 100mg (14 weeks), tildrakizumab 100mg (28 weeks).*

The optimal treatment based on NMB (vs BSC alone) is: *etanercept*

At a £30,000 per QALY threshold:

The following treatments are cost-effective compared to BSC alone: *adalimumab, etanercept, tildrakizumab 100mg (14 weeks), tildrakizumab 100mg (28 weeks),ustekinumab.*

The optimal treatment based on NMB (vs BSC alone) is: *tildrakizumab 100mg (28 weeks).*

The contrasting results show how critical the assumptions are surrounding both the costs but also the HRQoL of patients receiving BSC alone. Although the ranking results of Table 54 suggest that tildrakizumab 100mg (14 weeks) is the 2nd most efficient active treatment, this finding needs to be treated with caution since none of the active treatments appear more cost-effective than BSC alone. The rankings from Table 55 are more meaningful given that all the treatments identified in the optimal ranking appear more cost-effective than BSC alone.

These results from Table 55 also appear to support the company's conclusions regarding the potential cost-effectiveness of tildrakizumab. They also appear to further support the company's view that a longer induction and response assessment period for tildrakizumab (28 weeks) is potentially more cost-effective than a shorter period (14 weeks). However, despite providing some reassurance regarding the company's own conclusions, several important caveats also apply. Firstly that these conclusions only hold when a specific assumption is made concerning the HRQoL of people receiving BSC alone and secondly, that the confidential access schemes for the comparator treatments will not alter these rankings. Although the first assumption is uncertain, the results from the ERG's

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confidential appendix clearly show that the rankings of the comparators are significantly affected when their confidential discounts are applied.

The ERG highlights that these conclusions are based entirely on their alternative approach to evaluating sequences. The ERG now returns to the company's approach to sequence analysis and the use of fully incremental ICER's to determine the cost-effectiveness of tildrakizumab. The ERG's sequence comparison includes the same eight sequences included by the company but also includes two additional sequences including tildrakizumab 100mg (28 weeks) and infliximab.

In the fully incremental ICER comparison reported in Table 56, there were four non-dominated (dominance and extended dominance) sequences. Of these, the least effective and lowest cost was the sequence starting with etanercept (sequence 5). The ICER of the tildrakizumab 100mg (14 week) sequence (sequence 1) is £39,683 per QALY compared to the etanercept sequence. The ICER of the tildrakizumab 100mg (28 week) sequence is £40,470 per QALY compared to the tildrakizumab 100mg (14 week) week sequence. Finally, the ixekizumab sequence (sequence 6) was the most effective and most costly of the non-dominated sequences. The ICER of the ixekizumab sequence versus the tildrakizumab 100mg (28 week) sequence is £412,418 per QALY. The difference between the results of the company base case and the ERG base case were mainly due to different estimates of the cost of BSC.

In the fully incremental ICER comparison reported in Table 57, there were also four non-dominated (dominance and extended dominance) sequences. Of these, the least effective and lowest cost was the sequence starting with etanercept (sequence 5). The ICER of the tildrakizumab 100mg (14 week) sequence (sequence 1) is £21,612 per QALY compared to the etanercept sequence. The ICER of the tildrakizumab 100mg (28 week) sequence is £22,342 per QALY compared to the tildrakizumab 100mg (14 week) week sequence. Finally, the ixekizumab sequence (sequence 6) was the most effective and most costly of the non-dominated sequences. The ICER of the ixekizumab sequence versus the tildrakizumab 100mg (28 week) sequence is £254,261 per QALY.

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Table 56 ERG alternative base case: Fully incremental ICER comparison

Sequence	1st line	2nd line	3rd line	4th line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) fully incremental
5	ETN	UST	SEC	BSC	£163,907	[redacted]	[redacted]	[redacted]	NA
1	TIL 14wk	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£39,683
2	ADA	UST	SEC	BSC	£169,917	[redacted]	[redacted]	[redacted]	Dominated
3	UST	ADA	SEC	BSC	£170,447	[redacted]	[redacted]	[redacted]	Dominated
10	TIL28 wk	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£40,470
4	SEC	UST	ADA	BSC	£177,724	[redacted]	[redacted]	[redacted]	Dominated
9	INF	UST	SEC	BSC	£189,168	[redacted]	[redacted]	[redacted]	Ext. Dominated
8	GUS	UST	SEC	BSC	£197,100	[redacted]	[redacted]	[redacted]	Ext. Dominated
6	IXE	UST	SEC	BSC	£200,369	[redacted]	[redacted]	[redacted]	£412,418
7	BRO	UST	SEC	BSC	£203,330	[redacted]	[redacted]	[redacted]	Dominated

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Table 57 ERG alternative base case (including additional assumption that utility of BSC = baseline utility: Fully incremental ICER comparison

Sequence	1st line	2nd line	3rd line	4th line	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) fully incremental
5	ETN	UST	SEC	BSC	£163,907	[redacted]	NA	[redacted]	NA
1	TIL 14wk	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£21,612
2	ADA	UST	SEC	BSC	£169,917	[redacted]	[redacted]	[redacted]	Dominated
3	UST	ADA	SEC	BSC	£170,447	[redacted]	[redacted]	[redacted]	Dominated
10	TIL28 wk	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£22,342
4	SEC	UST	ADA	BSC	£177,724	[redacted]	[redacted]	[redacted]	Dominated
9	INF	UST	SEC	BSC	£189,168	[redacted]	[redacted]	[redacted]	Ext. Dominated
8	GUS	UST	SEC	BSC	£197,100	[redacted]	[redacted]	[redacted]	Ext. Dominated
6	IXE	UST	SEC	BSC	£200,369	[redacted]	[redacted]	[redacted]	£254,261
7	BRO	UST	SEC	BSC	£203,330	[redacted]	[redacted]	[redacted]	Dominated

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It is interesting that the different approaches to evaluating sequences appear to lead to similar conclusions concerning the cost-effectiveness of tildrakizumab. That is, both approaches suggest that tildrakizumab is potentially cost-effective when an assumption is made that the utility of people receiving BSC alone is the same as the baseline utility. Both approaches also suggest that a longer induction and response assessment period for tildrakizumab (28 weeks) appears more cost-effective than a shorter period (14 weeks).

Despite the reassurance in terms of the alternative approaches providing similar conclusions, the ERG reiterates their concerns regarding the appropriateness and validity of fully incremental ICERs in situations where partial sequence comparisons are presented and treatments that are not-cost-effective are included within the sequence. The ERG highlights that all the sequences compared by the company include at least 1 non-cost-effective treatment. Hence, while it is reassuring that both approaches provide similar conclusions, the ERG remains concerned regarding the appropriateness and validity of basing decisions on a fully incremental ICER in these situations. Finally, the ERG restates that the conclusions regarding the potential cost-effectiveness of tildrakizumab only apply when a specific assumption is made concerning the HRQoL of people receiving BSC alone and when the confidential access schemes for the comparator treatments are ignored.

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7 End of life

The intervention does meet the end of life criteria published by NICE.

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8 Overall conclusions

All three of the randomised trials of tildrakizumab appeared to be generally well-conducted. However, the reSURFACE trials' results suggest that the efficacy of tildrakizumab may not be fully realised in some patients by the 12 week primary time point used for both the trials.[5] The two reSURFACE trials had some limitations in terms of their generalisibility to the population likely to receive tildrakizumab in the NHS e.g. only around 20% of patients had previously been treated with a biologic, whereas in NHS practice it is very unlikely that tilradkizumab would be given as a first choice biologic. [5]

The ERG considers that the NMA was conducted appropriately.

[redacted]The results of the additional sensitivity analyses requested by the ERG (provided by the company in their clarification response) showed little difference from the main analysis.

The ERG considered the company's economic model submitted as part of the company's response to clarifying questions to meet the requirements of the NICE reference case and to be of sufficient quality. The company base case results and the most relevant sensitivity analyses were successfully replicated. The logical checks performed on the model (e.g. extreme values for costs and utilities, treatment efficacy inputs equalised across treatment and comparators) confirmed the model behaved logically. The ERG identified issues in the calculation of the age-adjusted utilities, which was addressed by the company at the clarification stage.

The ERG identified several areas of uncertainty regarding inputs and assumptions. The ERG also concludes that the restrictive nature of the sequences compared is an important limitation. The ERG proposes an alternative approach to inform the cost-effectiveness of alternative sequences based on net-benefit calculations and associated rankings of each individual treatment compared to BSC. Other key areas of uncertainty were length of the induction period for tildrakizumab (14 vs. 28 weeks), the source for the BSC cost, and the utilities applied to patients receiving BSC.

The uncertainties identified by the ERG were explored in 10 separate scenarios. An alternative ERG base-case was also undertaken combining changes based on 6 of the scenarios. The specific scenarios represented those scenarios the ERG consider provide more appropriate or plausible assumptions than the company base-case.

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The ERG concludes that both tildrakizumab 100mg 14 weeks and 28 weeks exceed NICE's conventional cost-effective thresholds. If there is strong support for the assumption that patients receiving BSC return to their baseline utility, both tildrakizumab options fall below the £30,000 threshold. However, these results exclude the confidential patient access schemes (PAS) for several comparators (brodalumab, guselkumab, ixekizumab and secukinumab). The impact of including these confidential PAS schemes is presented in a separate confidential appendix.

8.1 Implications for research

Any uncertainty regarding the efficacy of tildrakizumab relative to comparator biologics could be resolved with a randomised, blinded trial lasting at least 28 weeks. Long-term assessment for adverse events and rates of loss of efficacy is needed, preferably via an established biologics registry.

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10 Appendices

Appendix table: Treatment arms (by treatment) and time points for data collection

Treatment	Treatment arm	Trial name	Time point (weeks)	ICER	Primary endpt in trial**
Ustekinumab	Ustekinumab 45mg wk 0, 4, 12	ACCEPT	12	12	
	Ustekinumab 90mg wk 0, 4, 12				
	Ustekinumab 45/90mg wk 0, 4, 12	AMAGINE 2	12	12	
	Ustekinumab 45/90mg wk 0, 4, 12	AMAGINE 3	12	12	
	Ustekinumab 45mg wk 0, 4, 12	Igarashi et al 2012	12	12	
	Ustekinumab 90mg wk 0, 4, 12				
	Ustekinumab 45/90mg wk 0, 4, 12	CLEAR	12	16	16
	Ustekinumab 45mg wk 0, 4, 12	LOTUS	12	12	
	Ustekinumab 45mg wk 0, 4, 12	PEARL	12	12	
	Ustekinumab 45mg wk 0, 4, 12	PHOENIX 1	12	12	
	Ustekinumab 90mg wk 0, 4, 12				
	Ustekinumab 45mg wk 0, 4, 12	PHOENIX 2	12	12	
	Ustekinumab 90mg wk 0, 4, 12				
	Ustekinumab 45/90mg wk 0, 4, 12	ultIMMA-1	16	16	
	Ustekinumab 45/90mg wk 0, 4, 12	ultiMMA-2	16	16	
Etanercept	Etanercept 50mg BIW	ACCEPT	12	12	
	Etanercept 50mg BIW for 12 weeks then QW	FIXTURE	12	12	
	Etanercept 50mg QW	Gottlieb et al 2003	12		
	Etanercept 50mg QW	Leonardi et al 2003[4545]	12	12	
	Etanercept 50mg BIW				
	Etanercept 25mg QW				
	Etanercept 50mg QW	Liberate	16	16	
	Etanercept 50mg QW	Papp et al 2005	12	12	
	Etanercept 50mg BIW for 12 weeks then QW				
	Etanercept 50mg BIW for 12 weeks then QW	ReSURFACE 2	12	12	
	Etanercept 50mg QW	Tyring et al 2006	12	12	
	Etanercept 50mg BIW	UNCOVER-2	12	12	
	Etanercept 50mg BIW	UNCOVER-3	12	12	
	Etanercept 50mg QW	Van de Kerkhof et al 2008	12		
Adalimumab	Adalimumab 40mg Q2Wld	Asahina et al 2010	16	16	
	Adalimumab 40mg Q2W (no loading dose)				
	Adalimumab 80mg Q2Wld				

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Treatment	Treatment arm	Trial name	Time point (weeks)	ICER	Primary endpt in trial**
	Adalimumab 40mg Q2W	Bissonnette et al 2013	16		
	Adalimumab 40mg Q2W	CHAMPION	12	16	16
	Adalimumab 40mg Q2W	M02-528 (Gordon 2006) [46 46]	12	--	12
	Adalimumab 40mg QW				
	Adalimumab 40mg Q2W	REVEAL	16 + 12*	16	
	Adalimumab 40mg Q2W	VOYAGE 1	16	16	
	Adalimumab 80mg at wk 0, 40mg wk1, 40mg Q2W	VOYAGE 2	16	16	
	Adalimumab 40mg Q2W	X-PLORE	12	-	16
	Adalimumab 40mg Q2W	Zhang et al 2015	12	12	
Brodalumab	Brodalumab 210mg Q2W	AMAGINE 1	12	12	
	Brodalumab 140mg Q2W				
	Brodalumab 210mg Q2W	AMAGINE 2	12	12	
	Brodalumab 140mg Q2W				
	Brodalumab 210mg Q2W	AMAGINE 3	12	12	
	Brodalumab 140mg Q2W				
	Brodalumab 210mg Q2W	Nakagawa et al 2016	12	12	
	Brodalumab 140mg Q2W				
	Brodalumab 70mg Q2W				
	Brodalumab 210mg Q2W	Papp et al 2012	16	12	12
	Brodalumab 70mg Q2W				
	Brodalumab 140mg Q2W				
	Brodalumab 280mg Q4W				
Secukinumab	Secukinumab 300mg Q4W	CLEAR	12	16	16
	Secukinumab 300mg Q4W	ERASURE	12	12	
	Secukinumab 150mg Q4W				
	Secukinumab 300mg Q4W	FEATURE	12	12	
	Secukinumab 150mg Q4W				
	Secukinumab 300mg Q4W	FIXTURE	12	12	
	Secukinumab 150mg Q4W				
	Secukinumab 300mg Q4W	JUNCTURE	12	12	
	Secukinumab 150mg Q4W				
Guselkumab	Guselkumab 100mg Q8W	VOYAGE 1	16	16	

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Treatment	Treatment arm	Trial name	Time point (weeks)	ICER	Primary endpt in trial**
	Guselkumab 100 mg wk 0, 4, 12	VOYAGE 2	16	16	
	Guselkumab 100mg Q8W	X-PLORE	12	-	16
	Guselkumab 5mg Q12W				
	Guselkumab 15mg Q8W				
	Guselkumab 50mg Q12W				
	Guselkumab 200mg Q12W				
Apremilast	Apremilast 10mg BID	CORE (Papp 2012)	16		16
	Apremilast 20mg BID				
	Apremilast 30mg BID				
	Apremilast 30mg BID	ESTEEM 1	16	16	
	Apremilast 30mg BID	Liberate	16	16	
	Apremilast 20mg BID	Ohtsuki	16	16	
	Apremilast 30mg BID				
	Apremilast 30mg BID	UNVEIL	16		16
Ixekizumab	Ixekizumab 80mg Q4W	UNCOVER-1	12	12	
	Ixekizumab 80mg Q2W				
	Ixekizumab 80mg Q4W	UNCOVER-2	12	12	
	Ixekizumab 80mg Q2W				
	Ixekizumab 80mg Q4W	UNCOVER-3	12	12	
	Ixekizumab 80mg Q2W for 12 weeks then Q4W				
Tildrakizumab	Tildrakizumab 100mg wk 0,4	Papp 2015 P05495	16		16
	Tildrakizumab 200mg wk 0,4				
	Tildrakizumab 25mg wk 0, 4				
	Tildrakizumab 5mg wk 0, 4				
	Tildrakizumab 100mg wk 0, 4	ReSURFACE 1	12	12	12
	Tildrakizumab 200mg wk 0, 4				
	Tildrakizumab 100mg wk 0, 4	ReSURFACE 2	12	12	12
	Tildrakizumab 200mg wk 0, 4				
Risankizumab	Risankizumab 150mg wk 0, 4, 16, 28, 40	ultIMMA-1	16	16	
	Risankizumab 150mg wk 0, 4, 16, 28, 40	ultIMMA-2	16	16	
DMF	DMF maximum 720mg (240mg TID)	BRIDGE	16		16

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Treatment	Treatment arm	Trial name	Time point (weeks)	ICER	Primary endpt in trial**
	Fumaderm maximum 720mg (240mg TID)	BRIDGE	16		16

*- used in week 12 sensitivity analysis; ** only if tildrakizumab and ICER time points not the same

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