NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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

NICE National Institute for Health and Care Excellence

Tildrakizumab for treating moderate to severe plaque psoriasis [ID1060]

Pre-meeting briefing (part 1)

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

– the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
– the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

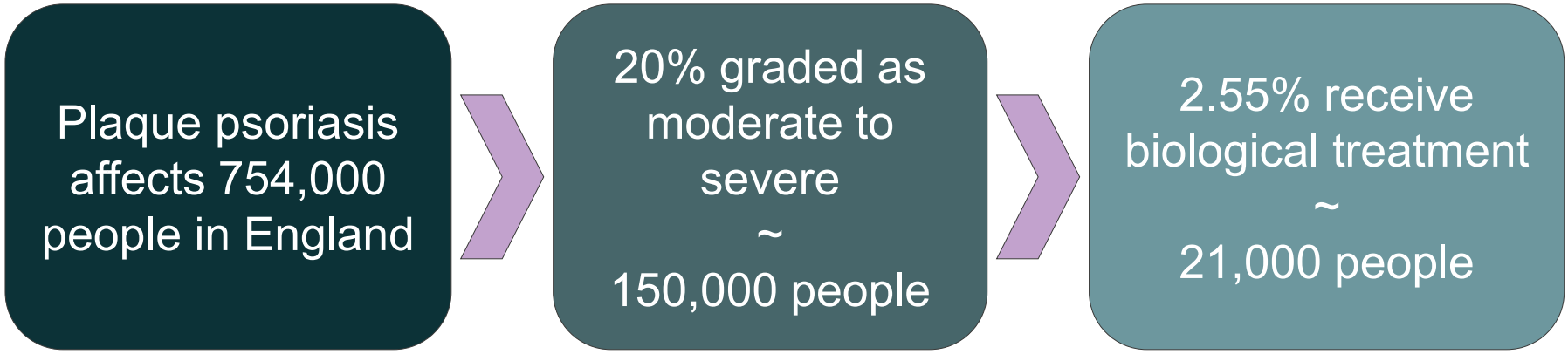
Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

[redacted]

Disease background

- Chronic inflammatory condition characterised by flaky, scaly, itchy and red plaques on skin
- May affect scalp, elbows, knees, lower back and sometimes face, groin, armpits and behind the knees
- Unpredictable, relapsing and remitting course
- Associated with comorbidities such as depression, anxiety, arthritis, cardiovascular disease
- Graded as mild, moderate or severe (based on location, area affected, severity of lesions and impact on individual)
- Population:



Patient and clinical perspective

Distressing and debilitating, need for a range of highly effective convenient treatments with minimal adverse reactions and impact on lifestyle

Impact of psoriasis

- can be distressing at all levels of severity
- affects all aspects of life: physical, psychological, social, financial
- topical medicines and phototherapy are inconvenient

People would like

- range of effective options (people respond differently to treatments)
- reduces symptoms immediately
- no adverse reactions
- limited impact on lifestyle
- targets high impact sites

Tildrakizumab

- convenient to administer every 12 weeks
- targeting of IL-23 pathway is recent innovation
- similar safety profile to other biological treatments

[redacted]

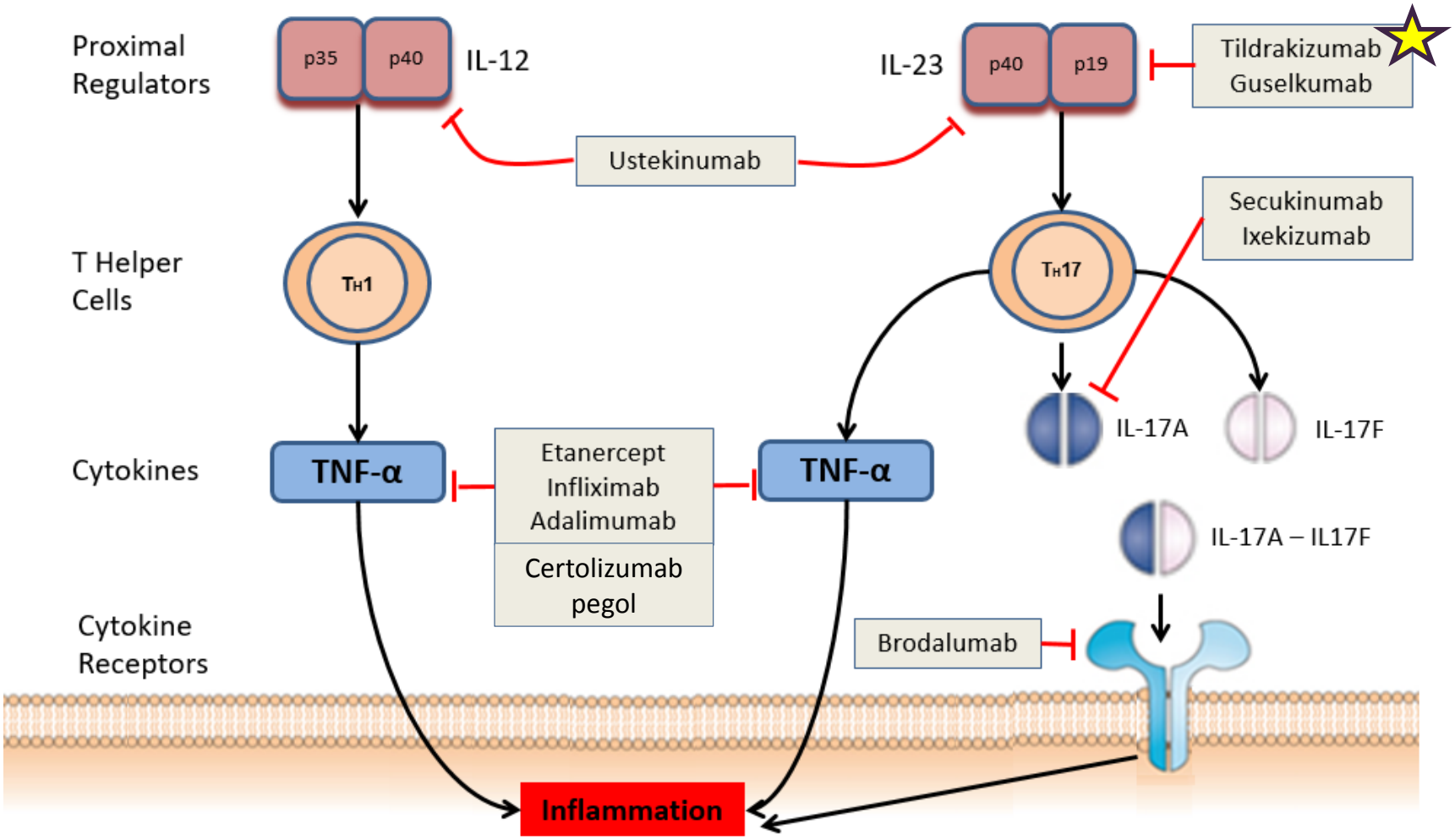
Tildrakizumab (Ilumetri®, Almirall)

Mechanism	• Tildrakizumab is a monoclonal antibody that is a selective inhibitor of the p19 subunit of interleukin-23. This inhibits inflammatory pathway in psoriasis biological mechanism
Marketing authorisation	• The marketing authorisation (October 2018) is for: "treatment of adults with moderate to severe psoriasis who are candidates for systemic therapy"
Administration and dose	• Subcutaneous injection of **100mg** at weeks 0, 4 and every 12 weeks thereafter • **200mg** dose may be appropriate for patients with certain characteristics (high disease burden, ≥90kg body weight), **both doses are presented** for this appraisal • Self-administration may be appropriate with training
List price	• A confidential discount to the list price has been agreed
Stopping rule	• Consideration should be given to discontinuing treatment in patients who have shown no response after 28 weeks of treatment

[redacted]

Biological mechanism

- Biological mechanism for development of psoriasis is complex and dynamic, involving skin cells and immune cells
- Current biological treatments selectively inhibit different signals within the inflammatory process to reduce the immune response
- People respond differently to different treatments and biological targets

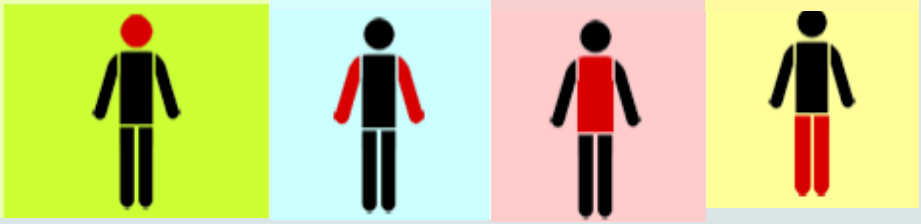


Measuring psoriasis severity and response

Psoriasis Area and Severity Index (PASI)

- Weighted score (0 to 72) of 4 affected areas (head, arms, trunk, legs)
  - 0 (no psoriasis); 10 (moderate); >10 (severe)
- Clinically important response: 75% reduction in PASI score from baseline (PASI 75). PASI 50, 90 and 100 are also considered in this appraisal.

	Head	Arms	Trunk	Legs
Area	○0% ○<10% ○10-29% ○30-49% ○50-69% ○70-89% ○90-100%			
Erythema (redness)	○0 ○1 ○2 ○3 ○4			
Induration (thickness)	○0 ○1 ○2 ○3 ○4			
Desquamation (scaling)	○0 ○1 ○2 ○3 ○4			



Physician Global Assessment (PGA)

- Physician's impression of psoriasis severity – 0 (clear) to 5 (severe)
- Clinically important response: 'clear' (0) or 'minimal' (1)

Dermatology Quality of Life Index (DLQI)

- 10 questions about how psoriasis affects quality of life: symptoms, feelings, daily activities, treatment etc.
  - Each question scores 0-3 (3 is the worst impact); >10 DLQI (severe)
- Clinically important response: 5-point reduction in DLQI

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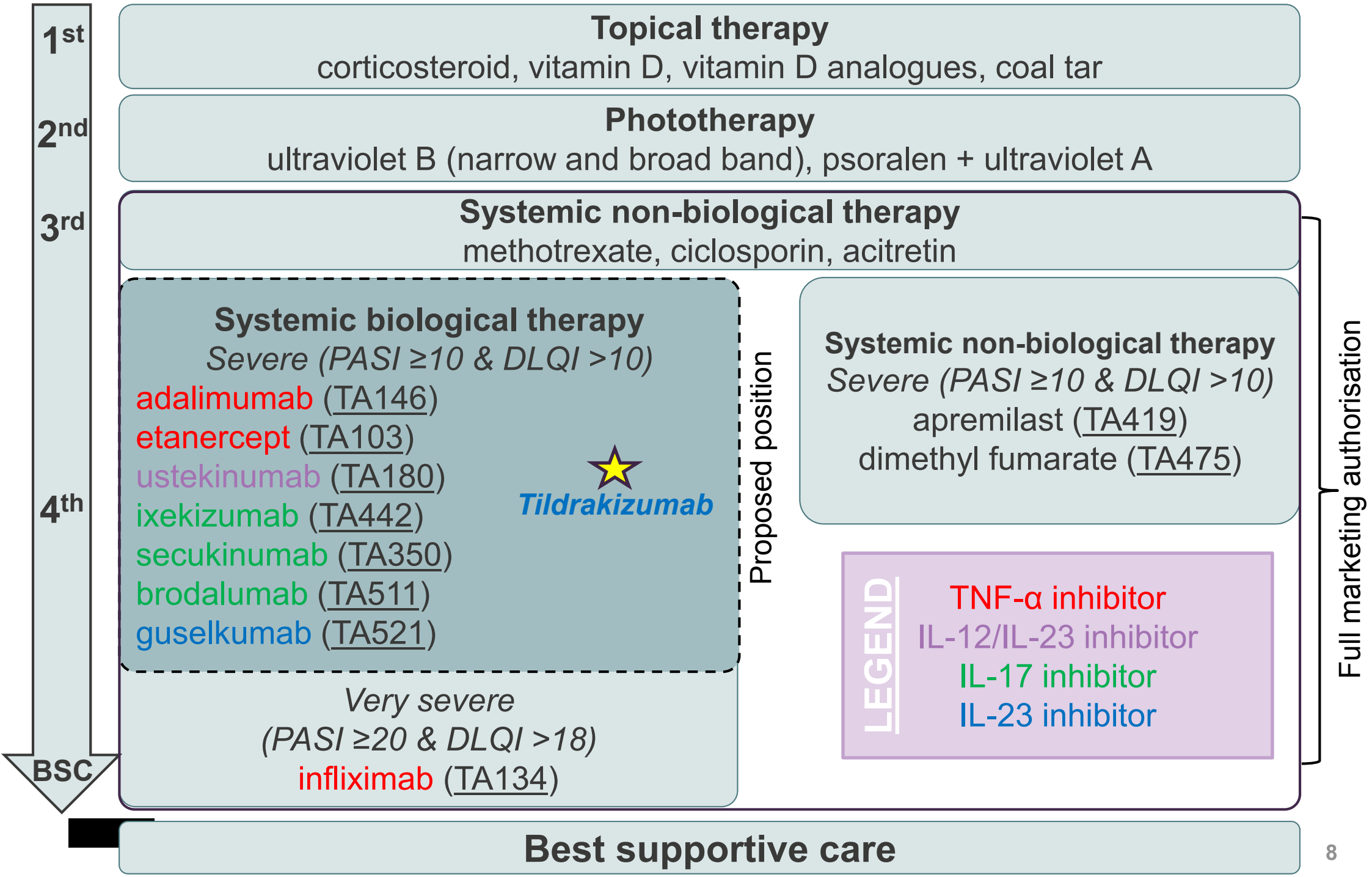
Treatment Pathway



Decision problem – population

NICE scope: "adults with moderate to severe plaque psoriasis"

Company's decision problem: adults with moderate to severe plaque psoriasis ***who are candidates for systemic therapy***

- **Company comment**: *"In clinical practice, tildrakizumab is expected to be used as an additional option alongside existing **biologic** treatment options"*

- Comparison to other biological treatments reflects likely position within UK clinical practice
- Effectively limits decision problem to adults with severe plaque psoriasis (PASI ≥ 10 and DLQI > 10)
- The inclusion criteria of clinical trials specified PASI score ≥ 12

[redacted]

Decision problem – intervention and comparators

	NICE scope	Company's decision problem
Intervention	Tildrakizumab	As per NICE scope for clinical effectiveness. Tildrakizumab in a treatment sequence followed by ustekinumab, secukinumab then best supportive care for economic analysis.
Comparators	• Systemic non-biological therapies • Phototherapy • 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* • Best supportive care	Current ***biological treatments only*** (severe): • Adalimumab • Brodalumab • Secukinumab • Ustekinumab • Etanercept • Ixekizumab • Guselkumab • Best supportive care As part of a treatment sequence in economic analysis (see slide 34)

- Decision problem population excludes systemic non-biological therapies and phototherapy as potential comparators (4th line equivalent)
- Apremilast and dimethyl fumarate would be used prior to or in patients unsuitable for biologics
- Infliximab is not considered a comparator as it is NICE recommended for very severe psoriasis

- ERG agrees that apremilast and dimethyl fumarate would not be used in clinical practice in preference to biological treatment but should have been included as comparators
- Infliximab should also have been included because very severe population should be included

Clinical evidence overview

reSURFACE1 and reSURFACE2

- Same study design: phase 3, international, randomised, double-blind, placebo-controlled trials
- Supports clinical ✓
- Supports safety ✓

reSURFACE1

- Dec 2012 to Oct 2015 (64 weeks duration); UK sites
- n=772
- tildrakizumab (100mg or 200mg) vs placebo

reSURFACE2

- Feb 2013 to Sept 2015 (52 weeks duration); no UK sites
- n=1090
- tildrakizumab (100mg or 200mg) vs placebo and **etanercept**

NCT01225731

- Phase 2b dose-finding study
- n=355 (n=175 at 100mg and 200mg licensed doses)
- tildrakizumab vs placebo
- Supports clinical X
- Supports safety ✓

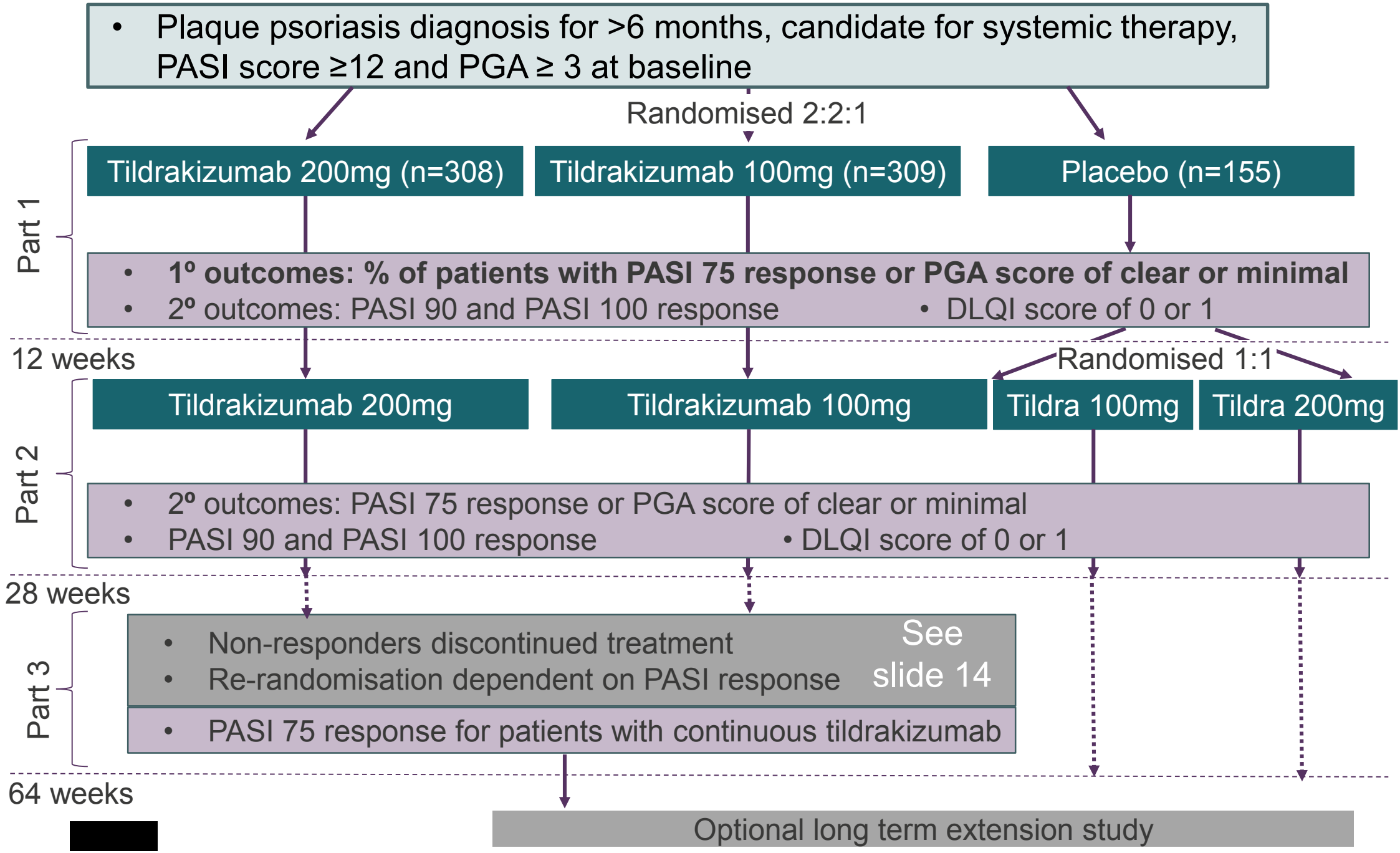
Network meta-analysis

Included 45 studies potential treatments

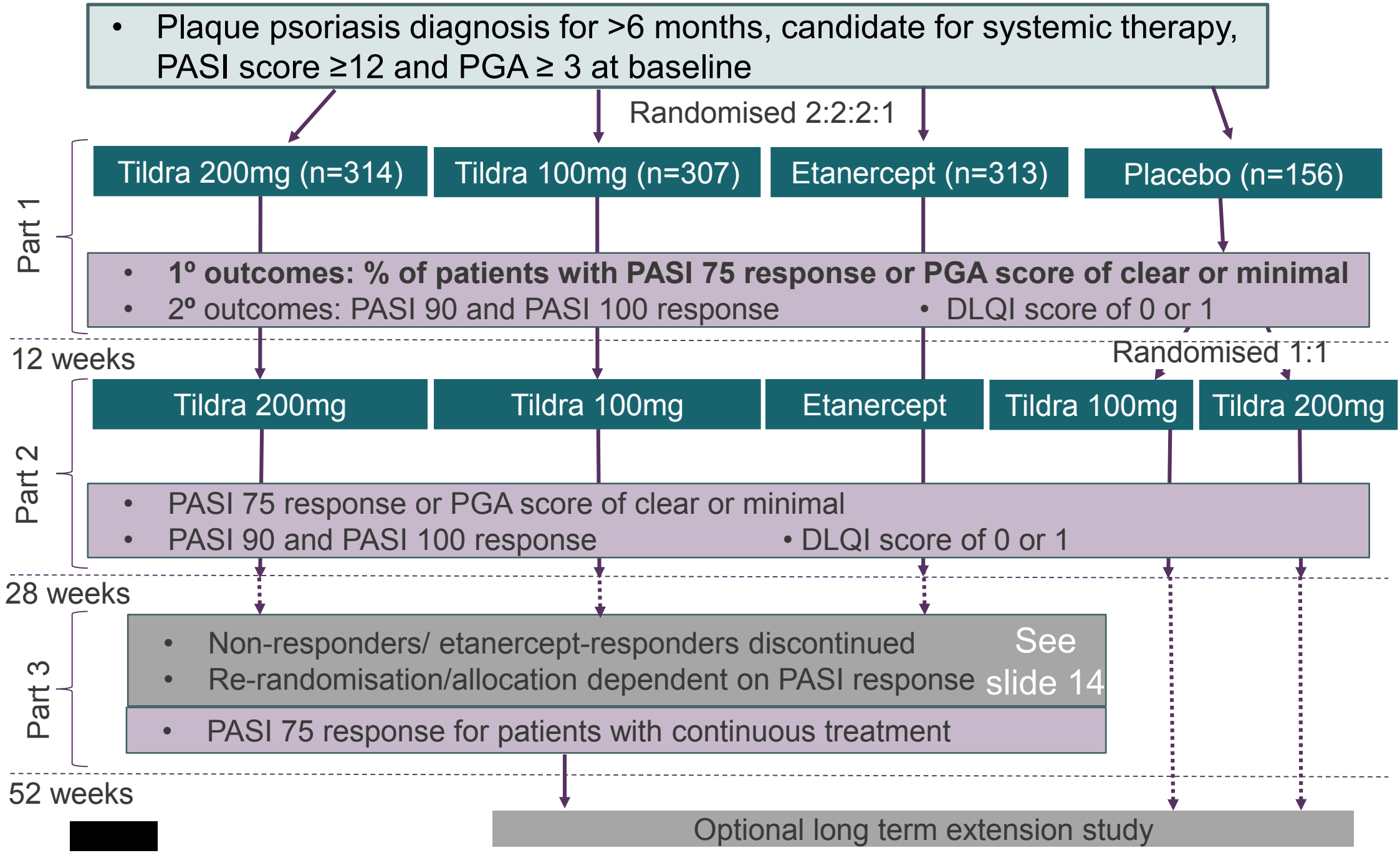
Used in the economic model ✓

[redacted]

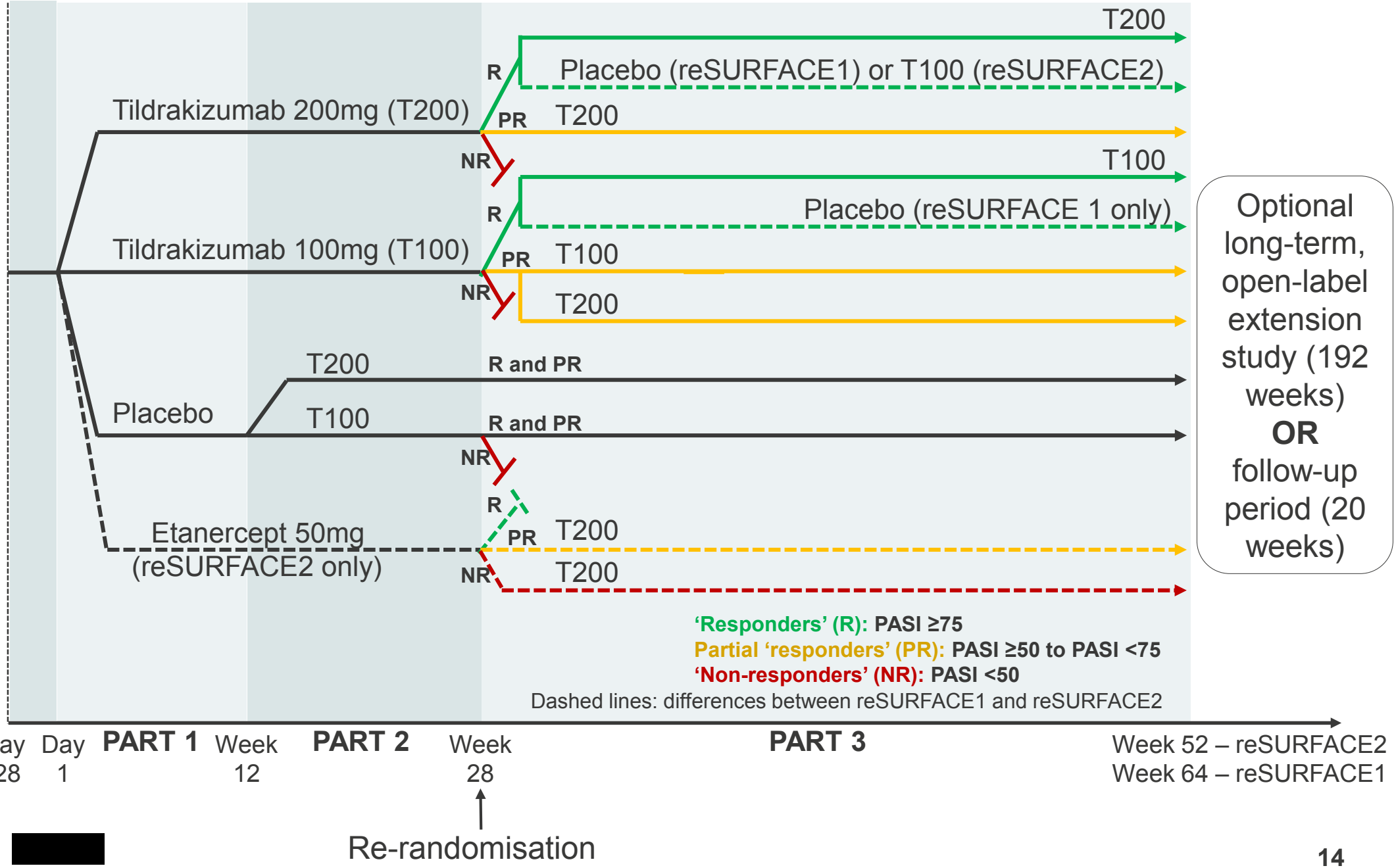
reSURFACE 1 study design



reSURFACE 2 study design



reSURFACE trials – re-randomisation



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Baseline characteristics

	reSURFACE 1			reSURFACE 2			
	Tildra 100mg (N=309)	Tildra 200mg (N=308)	Placebo (N=155)	Tildra 100mg (N=307)	Tildra 200mg (N=314)	Etanercept 50mg (N=313)	Placebo (N=156)
Male	207 (67%)	226 (73%)	100 (65%)	220 (72%)	225 (72%)	222 (71%)	112 (72%)
Age, years (SD)	46.4 (13.1)	46.9 (13.2)	47.9 (13.5)	44.6 (13.6)	44.6 (13.6)	45.8 (14.0)	46.4 (12.2)
Percent body surface area (SD)	29.7 (17. 4)	30.9 (17.8)	29.6 (17.3)	34.2 (18.4)	31.8 (17.2)	31.6 (16.6)	31.3 (14.8)
PASI score (SD)	20.0 (7.85)	20.7 (8.51)	19.3 (7.07)	20.5 (7.63)	19.8 (7.52)	20.2 (7.36)	20 (7.57)
DLQI (SD)	13.9 (6.7)	13.2 (6.9)	13.2 (7.3)	14.8 (7.2)	13.2 (7.0)	14.5 (7.2)	13.7 (7.0)
Previously treated with biologic	71 (23%)	71 (23%)	35 (23%)	39 (13%)	38 (12%)	37 (12%)	20 (13%)
Previously treated with non-biologic	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX

ERG comments – reSURFACE study designs

- The design of reSURFACE1 and reSURFACE2 are appropriate to inform questions about efficacy of tildrakizumab.
- But limited because the placebo controlled phase is limited to 12 weeks – after only two doses of tildrakizumab have been administered

Generalisability to NHS patients:

- ~20% previously had a biologic → tildrakizumab unlikely to be used as a first line biologic
- 20-40% across both trials previously had a non-biologic → most NHS patients are expected to have tried a non-biologic before starting biological therapy

Longer-term data are less robust due to:

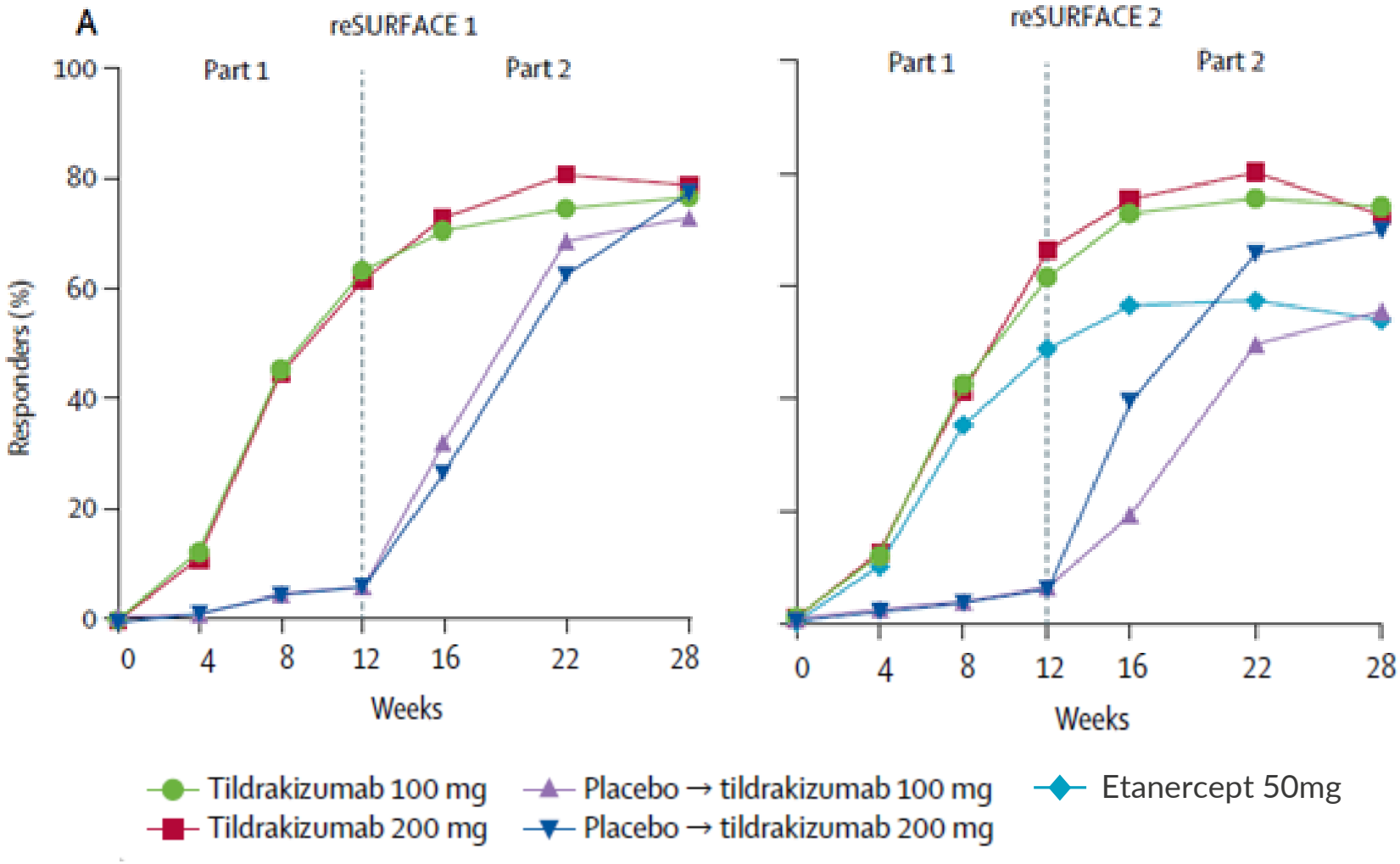
- a lack of control groups at longer time points
- a lack of blinding in the long-term phases (i.e. from week 52 or week 64)
- the use of 'as observed' datasets, which exclude many of the non-responders and dropouts

[redacted]

Primary endpoints (week 12)

Primary endpoint	reSURFACE 1			reSURFACE 2			
	Tildra 100mg (N=309)	Tildra 200mg (N=308)	Placebo (N=155)	Tildra 100mg (N=307)	Tildra 200mg (N=314)	Etanercept 50mg (N=313)	Placebo (N=156)
PASI 75							
Responders, N (%)	197 (63.8)	192 (62.3)	9 (5.8)	188 (61.2)	206 (65.6)	151 (48.2)	9 (5.8)
Difference from placebo, % (CI)	58.0 (51.0-64.1)	56.6 (49.6-62.8)	N/A	55.5 (48.3-61.8)	59.8 (52.9-65.9)	-	N/A
Difference from etanercept, % (CI)	-	-	-	13.1 (5.3-20.7)	17.4 (9.7-24.9)	N/A	-
Clear or minimal PGA							
Responders, N (%)	179 (57.9)	182 (59.1)	11 (7.1)	168 (54.7)	186 (59.2)	149 (47.6)	7 (4.5)
Difference from placebo, % (CI)	50.9 (43.6-57.4)	52.1 (44.8-58.5)	N/A	50.2 (43.2-56.5)	54.7 (47.9-60.8)	-	N/A
Difference from etanercept, % (CI)	-	-	-	7.3 (-0.5-15.0)	11.7 (4.0-19.3)	N/A	-

Proportion of patients achieving PASI 75



Secondary endpoints

	reSURFACE 1			reSURFACE 2			
	Tildra 100mg (N=309)	Tildra 200mg (N=308)	Placebo* (N=155)	Tildra 100mg (N=307)	Tildra 200mg (N=314)	Etanercept 50mg (N=313)	Placebo* (N=156)
Response at Week 12 (% responders)							
PASI 75	63.8	62.3	5.8	61.2	65.6	48.2	5.8
PASI 90	34.6	35.4	2.6	38.8	36.6	21.4	1.3
PASI 100	13.9	14.0	1.3	12.4	11.8	4.8	0
PGA clear or minimal	57.9	59.1	7.1	54.7	59.2	47.6	4.5
Response at Week 28 (% responders) (non-responder imputation)							
PASI 75	76.6	79.2	73.0 / 77.8	73.5	72.6	53.6	55.1 / 69.4
PASI 90	49.2	57.0	55.4 / 47.2	54.8	56.5	29.4	37.7 / 45.8
PASI 100	22.4	30.6	29.7 / 23.6	22.4	26.4	10.7	13.0 / 18.1
PGA clear or minimal	62.9	66.8	71.6 / 63.9	64.6	69.2	45.3	47.8 / 63.9

Placebo → tildrakizumab 100mg / Placebo → tildrakizumab 200mg at week 28*

[redacted]

ERG – stopping rule 12 weeks vs 28 weeks

- Summary of Product Characteristics states:
  "*Consideration should be given to discontinuing treatment in patients who have shown no response after 28 weeks of treatment*"
- Company comment:
  "*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 primary endpoints of both trials are measured at 12 weeks
- Economic analysis uses treatment assessment at 14 weeks
- ERG exploratory analysis to assess the impact of endpoints and assessment at 28 weeks

1

Considering the transitions between PASI groups at the two time points, many people who do not achieve PASI75 score at week 12 go on to achieve PASI75 by week 28. Results from pooled reSURFACE1 and 2 population who received tildrakizumab 100mg

[redacted]

[redacted] = ERG exploratory analysis

Subgroup analysis – PASI 75 at week 12

[redacted]

Previous systemic biological therapy	Yes
	No
Weight group	≤90
	>90
Previous systemic non-biological therapy	Yes
	No
Baseline PASI	<20
	≥20

[redacted]

Longer-term clinical effectiveness

Long-term efficacy for patients who responded well to treatment with a PASI 75 response at 28 weeks –

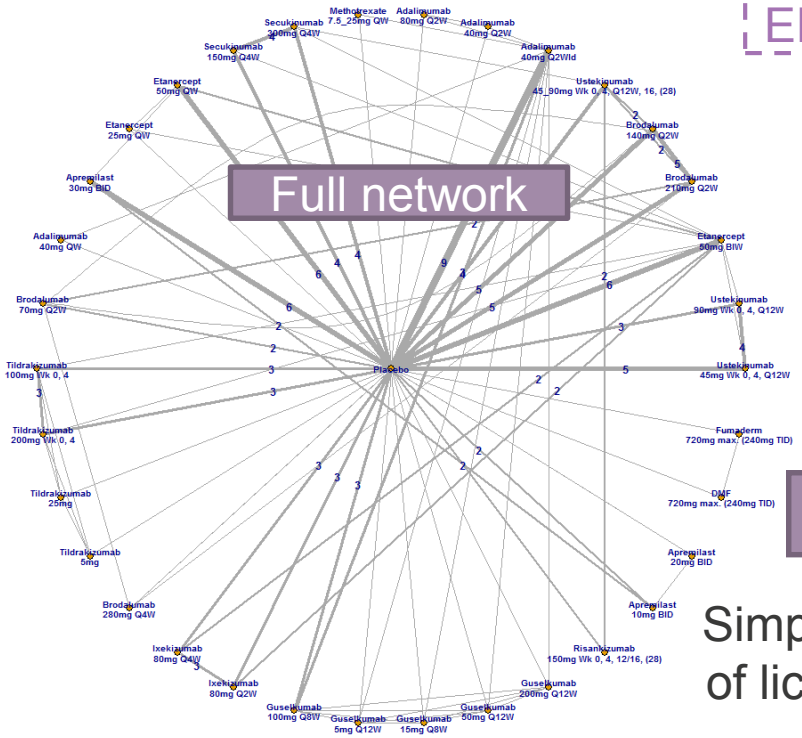
Tildrakizumab impact on quality of life

- Quality of life was measured through the proportion of people with a DLQI score of 0 or 1 in both studies
- reSURFACE1 also measured EQ-5D as an exploratory endpoint (used in economic analysis)

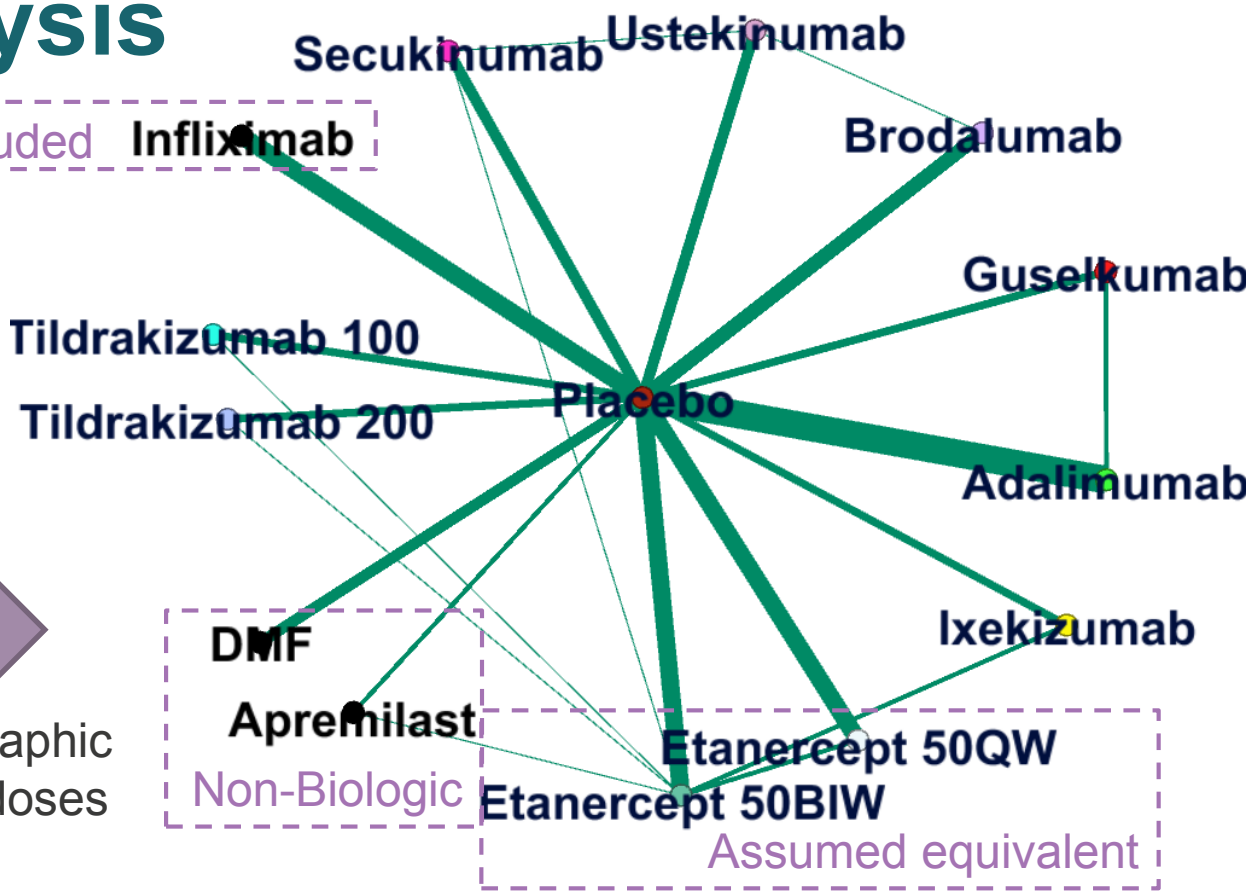
	reSURFACE 1			reSURFACE 2			
	Tildra 100mg	Tildra 200mg	Placebo*	Tildra 100mg	Tildra 200mg	Etanercept 50mg	Placebo*
DLQI score of 0 or 1 (% responders)							
Week 12	41.4	44.1	5.3	40.2	47.4	35.5	8.0
Week 28	52.4	56.7	52.1 / 56.9	54.1	65.0	39.4	38.2 / 56.5
	For PASI 75 responders at week 28			For PASI 75 responders at week 28			
Week 64/52**	52.2	68.4	-	68.8	72.4	-	-

Placebo → tildrakizumab 100mg / Placebo → tildrakizumab 200mg at week 28*
reSURFACE1 64 weeks, reSURFACE2 52 weeks**

Network meta-analysis



Simplified graphic of licensed doses



- A network analysis was performed to compare tildrakizumab with other biological treatments
- 45 studies were included in full network, using unlicensed doses, apremilast and dimethyl fumarate to enable a more complete network
- Outcomes measured were PASI 50, PASI 75, PASI 90 and PASI 100
- Measured outcome at between 12-16 weeks (Stage I - induction period in economic model) and 24-28 weeks (Stage III – part 2 of the trial, uses placebo data from 12-16 weeks)

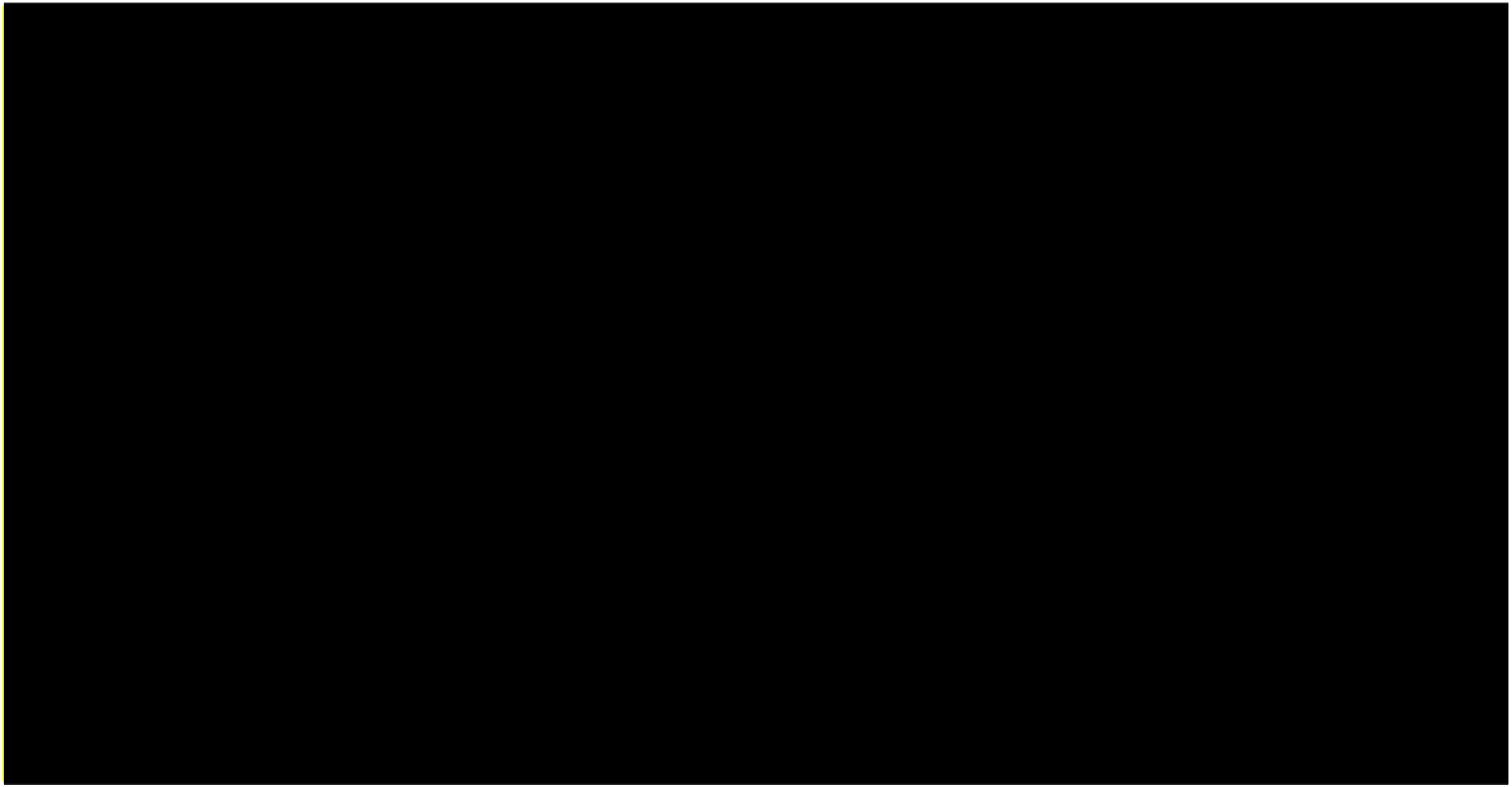
[redacted]

Network meta-analysis results

Tildrakizumab 100mg at week 12/16, random effects model PASI 75 forest plot

Comparison of 12/16 weeks vs 24/28 weeks

Forest plot of PASI 75 – treatment vs placebo: consistent across all comparators that it is more efficacious at week 24/28



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Stopping rules by treatment

- ERG noted instances in network meta-analysis that used the time point that was not the usual time point for that treatment (shown below)
- For example, 2 trials for adalimumab use 12 week data
- However, data show only very slight improvement between 12 and 16 weeks

TA number	Technology	Assessment made at:	Adequate response defined as:
TA103	Etanercept	12 weeks	• PASI 75 (75% reduction in PASI score from baseline) Or • PASI 50 + 5 point reduction in DLQI
TA350	Secukinumab		
TA442	Ixekinumab		
TA511	Brodalumab		
TA146	Adalimumab	16 weeks	
TA180	Ustekinumab		
TA521	Guselkumab		

[redacted]

ERG comment – network meta-analysis

- Network meta-analysis not in line with NICE scope (excludes infliximab) and not in line with company's decision problem (includes apremilast, DMF, risankizumab)
- ERG notes that infliximab is used for very severe psoriasis (PASI ≥20)
- Infliximab trials may strengthen the network, despite limited use in clinical practice and in a more severe subgroup
- For consistency with other appraisals, it should be included as a comparator and infliximab trials included in the network – this is included in ERG exploratory analysis
- Results for company-excluded comparators are included below

2

Forest plot of PASI 75 efficacy vs placebo with expanded network comparators

Safety data at 12 weeks (placebo-controlled)

- Adverse event data were pooled from the 3 available tildrakizumab studies
- Tildrakizumab was well tolerated with low rates of adverse events

	Tildrakizumab 100mg	Tildrakizumab 200mg	Placebo	Etanercept 50mg
Patients, N	705	708	355	313
Treatment-emergent adverse event (%)	340 (48.2)	339 (47.9)	191 (53.8)	169 (54.0)
Treatment-related adverse events (%)	104 (14.8)	99 (14.0)	47 (13.2)	92 (29.4)
Serious adverse events (%)	10 (1.4)	16 (2.3)	6 (1.7)	7 (2.2)
Treatment-related serious adverse events (%)	0	3 (0.4)	0	2 (0.6)
Discontinued due to treatment emergent adverse events (%)	4 (0.6)	9 (1.3)	4 (1.1)	6 (1.9)
Discontinued due to treatment-related adverse events (%)	1 (0.1)	3 (0.4)	2 (0.6)	4 (1.3)

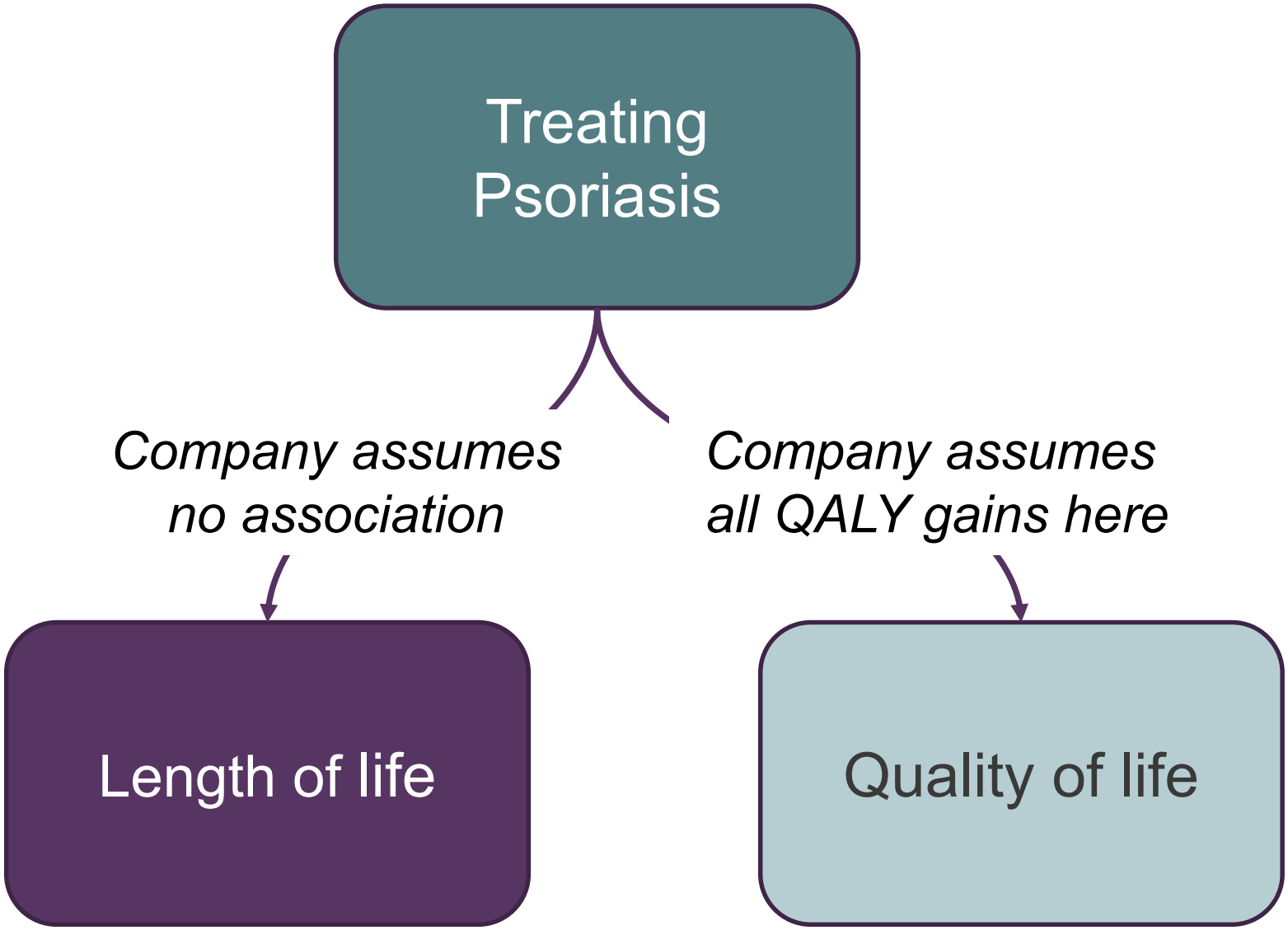
Key issues – clinical effectiveness

- What it the likely position of tildrakizumab in the treatment pathway for psoriasis in NHS clinical practice?
- What are the relevant comparators? Should apremilast, dimethyl fumarate and infliximab be included?
- Are the results from the reSURFACE trials generalisable to the eligible population in the NHS?
- When should clinical assessment on tildrakizumab occur? At:
  - 12 weeks (placebo-controlled clinical evidence)
  - 28 weeks (Summary of product characteristics stopping rule)
- Is the network meta-analysis suitable for decision-making?
  - Should infliximab be included in the network?
- Is tildrakizumab clinically effective?

[redacted]

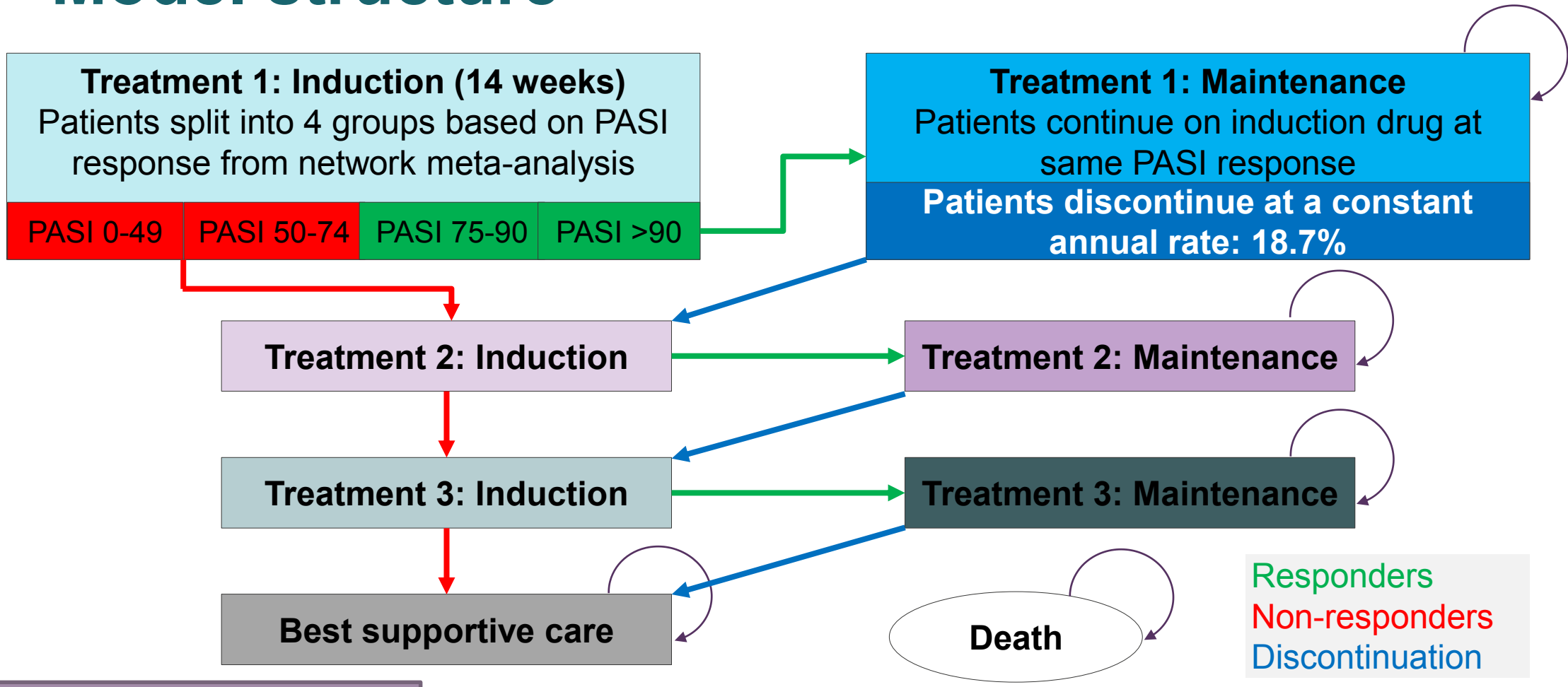
Cost-effectiveness

Where do QALY gains come from?



Increase in QALYs comes only from improvement in quality of life, rather than increasing length of life

Model structure



- Lifetime time horizon
- 14-week cycle length (half-cycle corrected)
- No adverse events
- 3.5% discount rate
- NHS/PSS perspective

- Markov state transition model: patients receive a **sequence of treatments**, switching after non-response (see next slide)
- Induction period response based on network meta-analysis PASI results at 12-16 weeks
- Mortality is independent of PASI, based on age-dependent mortality rates of the general population

Treatment sequences

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

- Based on British Association of Dermatologists guidelines
- Selected to include each treatment as the first in sequence
- Sequence 2 is most likely in clinical practice
- Unlikely to switch patient to a less effective treatment

LEGEND

TNF-α inhibitor
IL-17 inhibitor
IL-12/IL-23 inhibitor
IL-23 inhibitor

- ERG comments that the choices of treatment (1st in sequence) do not include infliximab, this is included in subsequent ERG analysis
- There is further justification for why apremilast and dimethyl fumarate were not included:
  - Apremilast would not displace biological therapy in the treatment pathway
  - Dimethyl fumarate is highly immunosuppressive
- Additionally, for consistency with TA521, ERG agreed with exclusion of these 2 treatments

ERG comments – treatment sequences

- Modelling 3 treatment lines followed by best supportive care in a sequence is consistent with clinical practice and modelling in previous NICE appraisals
- Previous appraisals have identified that the particular treatment sequences chosen do not always represent clinical practice
  - British Association of Dermatologist guidelines recommend adalimumab or ustekinumab first line, secukinumab has increased use at first line
  - Subsequent treatments are based on increased efficacy – not all sequences follow this rule
  - Selective sequences may provide misleading cost-effectiveness estimates about the technology of interest if treatments within the sequence are not cost-effective
  - Best supportive care at the end of sequence can result in change to the model logic (see slide 43)
- TA511 ERG proposed net-benefit calculations of individual treatments compared to best supportive care (net monetary benefit framework, see next slide)
- Treatment sequence could then be inferred from associated ranking
- This method was repeated for this appraisal in an exploratory analysis

[redacted]

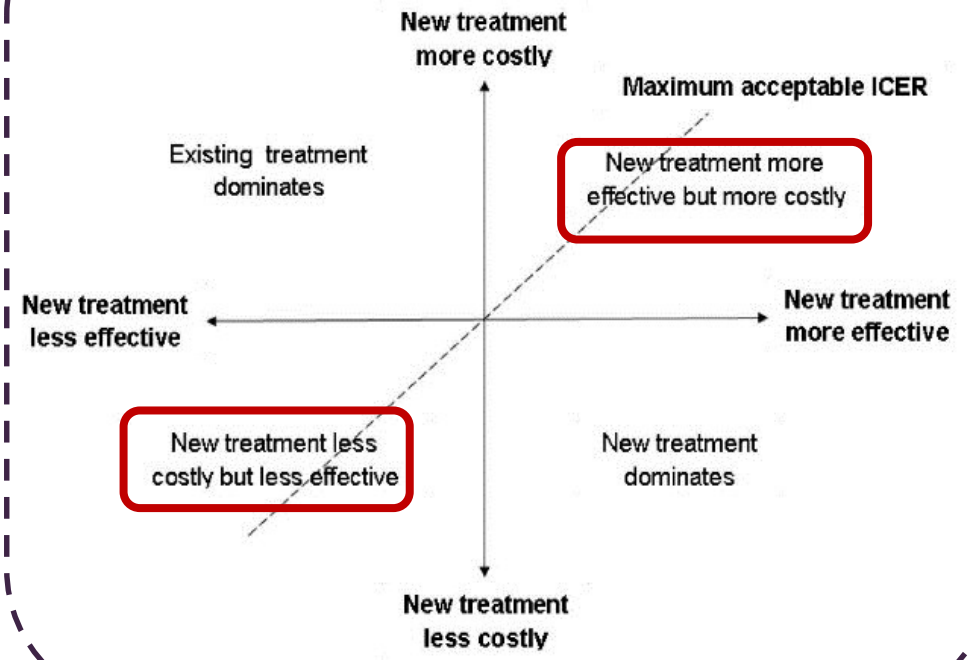
Incremental cost-effectiveness ratios (ICERs) vs net monetary benefit framework (NMB)

ICER: What is the extra cost per unit of extra benefit?

ICER decision rule: recommend technology if

Δ Costs/ Δ QALYs < threshold

But, ICER > 0 can mean:



NMB

- Value of an intervention in monetary terms at a willingness-to-pay threshold (NHS opportunity cost)
- For NMB, ICER decision rule is rearranged:

(Δ QALYs * threshold) – Δ Costs > 0

- Incremental NMB: difference in NMB between alternative interventions
- Positive incremental NMB: intervention is cost-effective compared with alternative at given willingness-to-pay threshold

14-week induction period

- The 14-week induction period and cycle length were chosen to simplify the model by representing the midpoint of the range of induction periods

Drug	Duration	Source
Adalimumab	16 weeks	NICE TA 455
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

[redacted]

- ERG disagrees with the company's justification for creating a common 14-week induction period for all treatments
- Creates bias in the costs of the induction period – dependent on frequency of administration – dependent on mismatch from 14 weeks
- Additional uncertainty given the stopping rule of 28 weeks is recommended in the summary of product characteristics
- Explored modelling costs from treatment-specific induction periods for their recommended duration

Proportion of patients achieving PASI response

- Data informed by relative risks in NMA

Treatment	Proportion of patients achieving PASI response (100mg)		
	≥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%
Best supportive care (placebo arm)	16.06%	6.00%	1.25%

- Used to estimate adequate response (state transition)
- Quality of life utility value stratified by PASI response

[redacted]

Source of utilities – ERG corrected

- Health related quality of life has been modelled with adjustment for age
- EQ-5D data from reSURFACE1 trial measured utility stratified by PASI score
- Utility values were originally derived from EQ-5D valuations from non-UK value sets. UK value set used after clarification
- Mean change from baseline was calculated for each PASI response subgroup
- Mean utility change (age-adjusted to PASI response subgroup) used to calculate a percentage change (programming error corrected by ERG)
- Percentage change applied to age-specific population norm for the cohort with a mean age in the trials of 46 (this norm varies over time)

State		Final EQ-5D utility value	Mean change	Mean change (age-adjusted)	Percentage change	Population utility norm (age 46)
Baseline		[redacted]				
PASI score	<50					
	≥50 to <75					
	≥75 to <90					
	≥90					

[redacted]

ERG comments – source of utilities

Appropriate utility values

- Utility values from reSURFACE1 appear appropriate when compared with results from a recent review of psoriasis treatments from the Institute for Clinical and Economic Reviews (I.C.E.R.) (table below)

State		reSURFACE1 utility value	(I.C.E.R.) utility value
Baseline		[redacted]	0.66
PASI score	<50		0.72
	≥50 to <75		0.83
	≥75 to <90		0.86
	≥90		0.90

Adjusting for age is not necessary

- Noted a number of issues with the company's age-adjustment :
  - A programming error
  - Assumes proportional relationship between age and impact of each PASI category
  - Assumes annual linear decrement
  - No utility decrements beyond age 76
- Company offered no justification for a multiplicative (proportional to age) approach compared to an additive approach
- There is no differential mortality effect between sequences or PASI score so there is no need for an age adjustment
- ERG performed an exploratory scenario that excluded age adjustment and used absolute utilities from reSURFACE1

5

[redacted]

ERG comment – best supportive care utility

- Company model uses utility from the PASI <50 response group to inform utility on best supportive care ([redacted])
- Uncertain whether these values can be generalised to patients not receiving biological therapies
- ERG suggests that baseline utility may give a more accurate representation of best supportive care utility ([redacted])
- Included in an exploratory analysis
- This assumption is a key driver of cost-effectiveness results (see slide 43)

6

[redacted]

Modelling assumptions - summary

Assumption	Justification	Consistent with previous appraisals	ERG approved
Markov model structure with treatment sequences	Allows for sequencing of treatment over an extended time horizon and incorporation of PASI responses from network meta-analysis	✓	X
14-week cycle length	Midpoint of the 12-16 week induction periods in most biological comparators	X	X
Common 14-week induction length for each treatment	Use of data from 12-16 week induction period from network meta-analysis simplified model structure	X	X
Position of treatment in sequence does not impact on effectiveness	PASI response may be lower further in the treatment sequence, evidence for this is variable – one study found no association	✓	✓
Discontinuation is fixed at 18.7% for all treatment options	Discontinuation may occur due to loss of efficacy or development of contraindication, assumed to be uniform across treatments	✓	✓

[redacted]

Best supportive care costs

- Company base-case best supportive care costs were based on values in the cost-effectiveness model for NICE guideline CG153
- Costs included drug therapy, phototherapy, day centre care and inpatient care
- Results uncertain due to a lack of recent studies to quantify true cost in clinical practice
- Total cost: **£3,088 per 14 week cycle**

- ERG notes previous appraisals TA442 and TA511 have discussed sources of best supportive care data and used data from Fonia et al (2010) observational study
- ERG concluded estimates were likely to be closer to (Fonia et al, 2010), adjusted for inflation
- Total costs: **£1,422 per 14 week cycle**
- These costs were incorporated in exploratory analysis

- This change in best supportive care costs leads to a change in model logic → best supportive care becomes the most cost-effective treatment → the least effective treatments within sequences are favoured because they decrease the time it takes to switch to best supportive care
- These assumptions, alongside values used for best supportive care utility (slide 41), are key drivers of cost-effectiveness

[redacted]

Non-responder costs

- Company base-case does not include any additional healthcare costs for patients who fail to respond to biological treatment and switch to another treatment or best supportive care
- Company presented a scenario analysis with additional costs of **£229 once per induction cycle** for those that fail to achieve PASI75
- Costs were based on TA442 and TA475 appraisals

- ERG considers non-responder costs justified and consistent with previous appraisals
- However, ERG assumed costs would be based on cycle length instead of one-off cost per induction period
- ERG adjusted costs to match cycle length: **£802 per 14-week induction cycle**
- ERG included these costs in exploratory analysis

[redacted]

Drug acquisition costs – ERG revised

Drug	List price	Induction period cost	Maintenance period cost
Tildrakizumab	£XXXX	£XXXX	£XXXX
Etanercept (biosimilar)	£322	£1,931	£2,252
Adalimumab (biosimilar available soon)	£704	£3,521	£2,465
Ustekinumab	£2,147	£4,294	£2,503
Secukinumab	£1,219	£7,313	£3,938
Ixekizumab	£1,125	£7,875	£3,938
Brodalumab	£1,280	£4,480	£4,480
Guselkumab	£2,250	£6,750	£3,938
Infliximab	£377	£5,655	£3,299

[redacted]

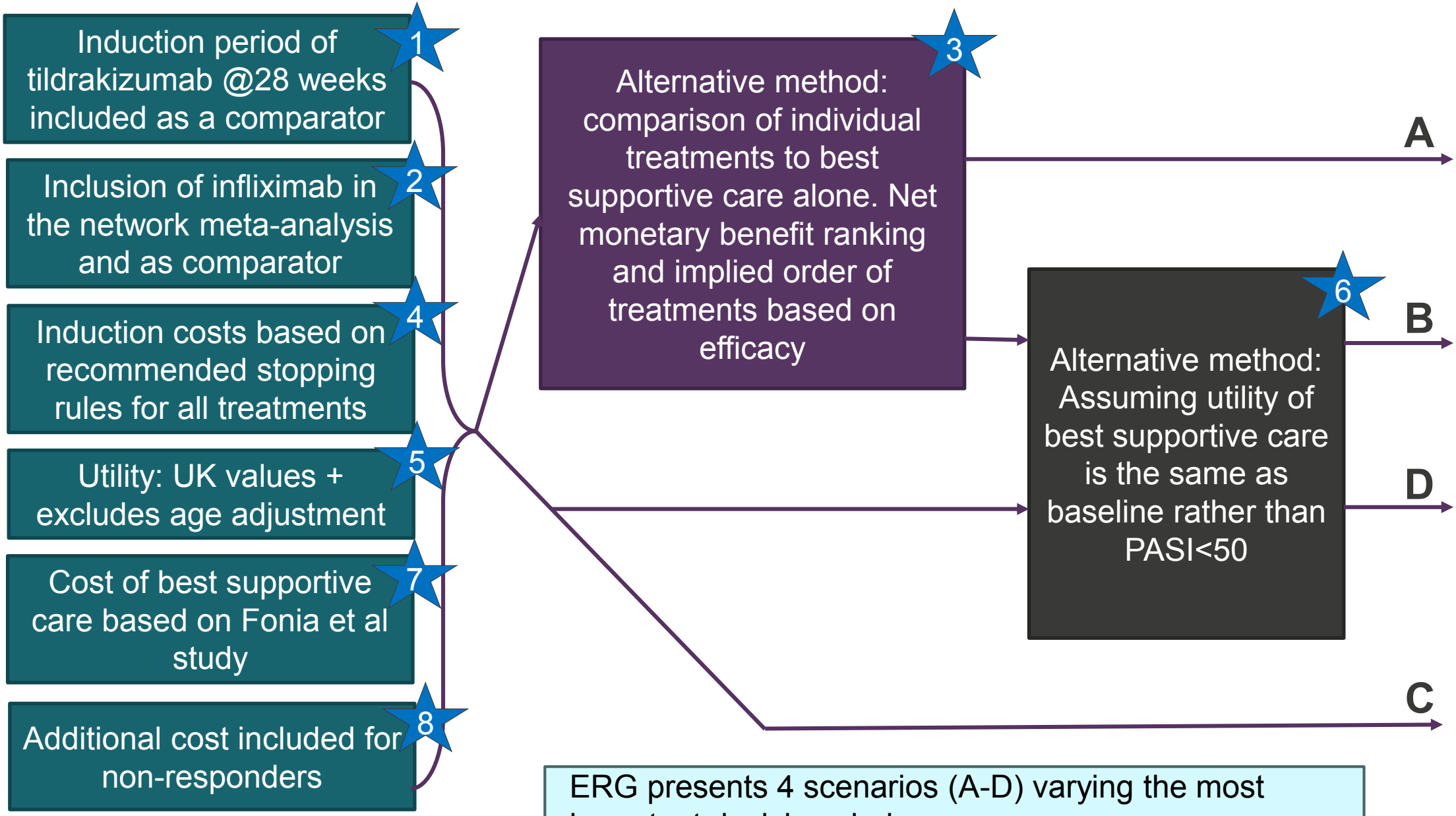
Confidential PAS discount available (not shown)

- ERG notes that induction costs were adjusted to 14-week induction length (see slide 37)
- ERG adjusted to reflect recommended induction period for each comparator drug as part of exploratory analysis
- ERG could not replicate the company's approach to estimate maintenance costs for comparator drugs, as company did not provide calculations
  - Newly calculated by ERG
- Revised inputs are incorporated into exploratory analysis
- Biosimilar costs for etanercept were considered by the company
- Adalimumab biosimilars have also become available to NHS recently

Costs and resource use - summary

Cost/Resource use	Source	Consistent with previous appraisals	ERG approved
Drug acquisition costs	List prices from BNF, separated by induction/maintenance stages, confidential discount prices included in ERG analysis	✓	X
Administration costs	Not modelled, assumed to be the same across treatments (subcutaneous injection)	✓	✓
Monitoring costs and resource use	NHS reference costs 2016/2017, in line with NICE clinical guideline (CG153)	✓	✓
Best supportive care costs	Cost-effectiveness model in NICE clinical guideline (CG153)	X	X
Non-responder costs	None modelled	X	X
Adverse event costs and resource use	None modelled. Tildrakizumab is well-tolerated (see safety data slide)	X	✓

ERG scenario analyses



ERG presents 4 scenarios (A-D) varying the most important decision choices

[redacted]

Results with cPAS in PMB part 2

No company base case results presented because there are confidential patient access schemes available for brodalumab, ixekizumab, secukinumab and guselkumab.

[redacted]

Innovation

Company comment:

- Tildrakizumab is a high-affinity anti IL-23p19 monoclonal antibody, which offers potential for improved targeting when compared with dual inhibition of both IL-12 and IL23 (ustekinumab)
- Low frequency of maintenance dosing (every 12 weeks) offers a convenient dosing regime that can help meet the needs of patients seeking to minimise disruption to daily life

Equality

Consultee comments:

- PASI may underestimate disease severity in people with darker skin (type IV-VI) as redness may be less evident (a key component of the PASI)
- DLQI will underestimate impact in people who are not sexually active, or older (retired) or socially isolated; it does not capture anxiety and depression

[redacted]

Key issues – cost effectiveness

- Should cost effectiveness be assessed using treatment sequences or comparing single agents?
- Which interpretation of cost-effectiveness analysis is preferred?
  - fully incremental/ pairwise incremental analysis (ICERs)
  - ranking through net monetary benefit framework
- Is it reasonable to apply trial outcomes at 12-16 weeks to a response assessment at 14 weeks in the model?
- What is the health-related quality of life of people on BSC following 3 lines of biological therapy?
- Should health-related quality of life be adjusted for age?
- Should cost of best supportive care be modelled using the company's approach or use consistent methods with previous appraisals?
- How should the costs of biosimilars to adalimumab be accounted for?

[redacted]

Authors

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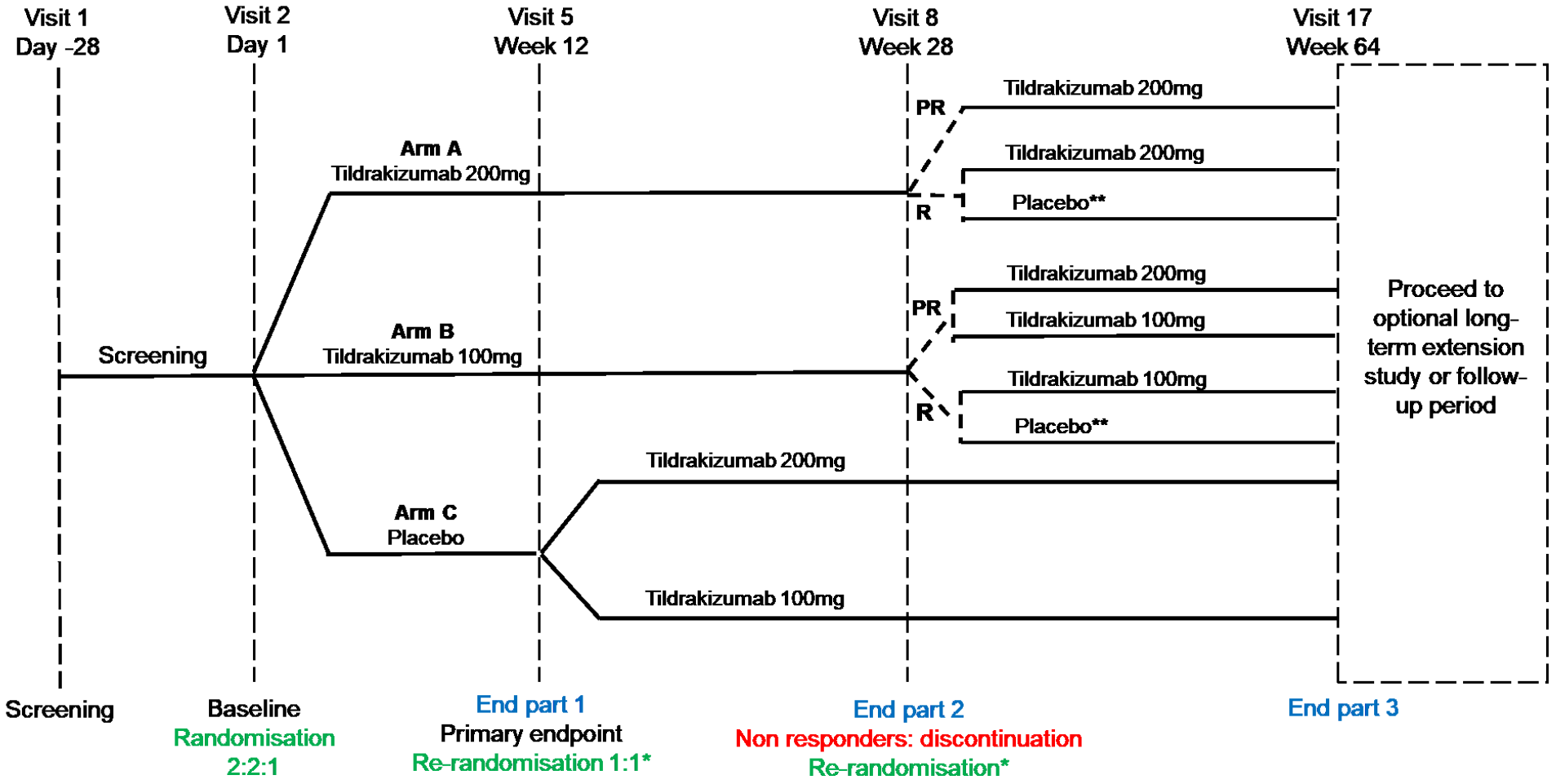
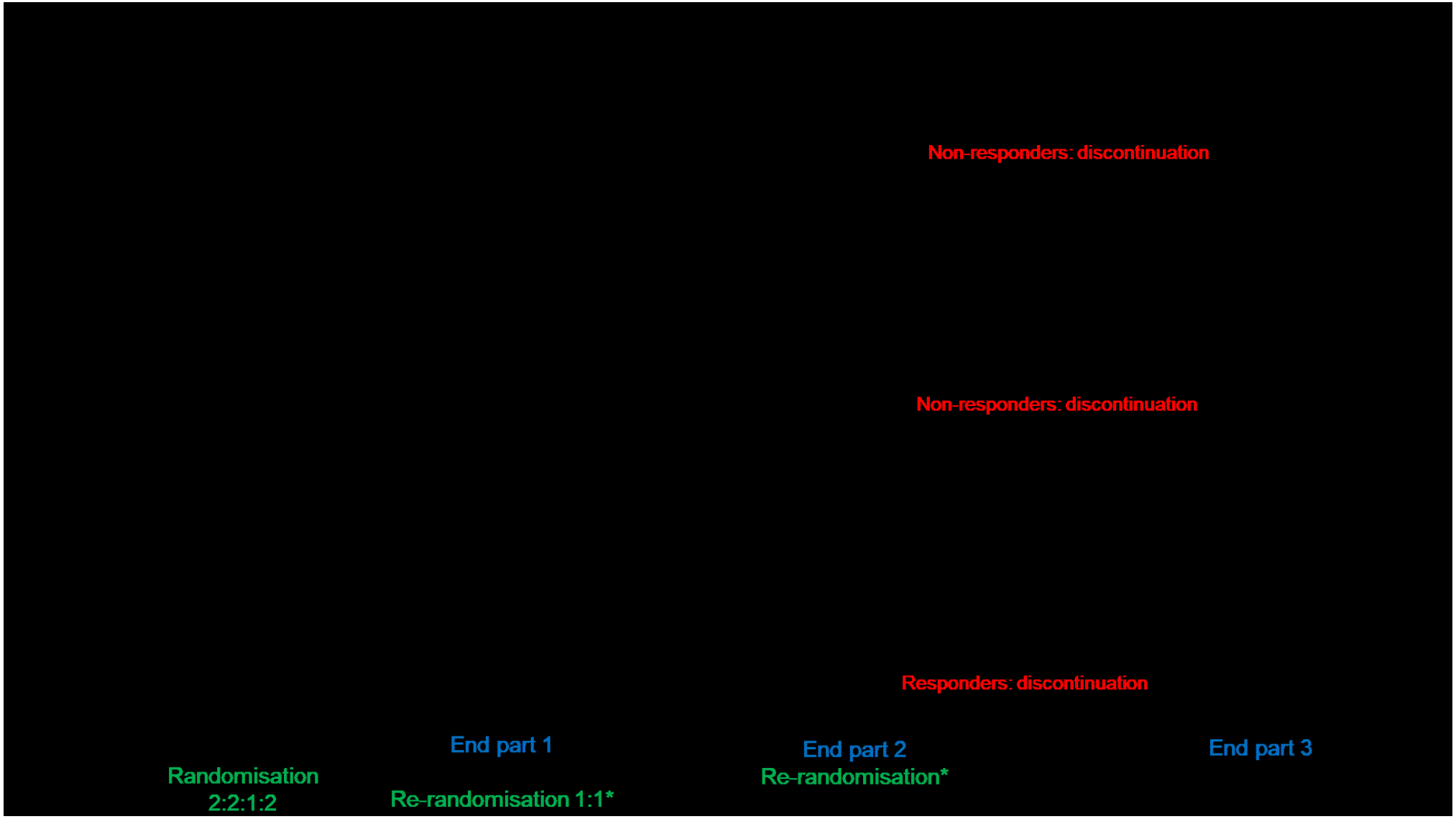
with input from the Lead Team (Stephen Smith and Sarah Wild)

Additional slides (non-essential reading)

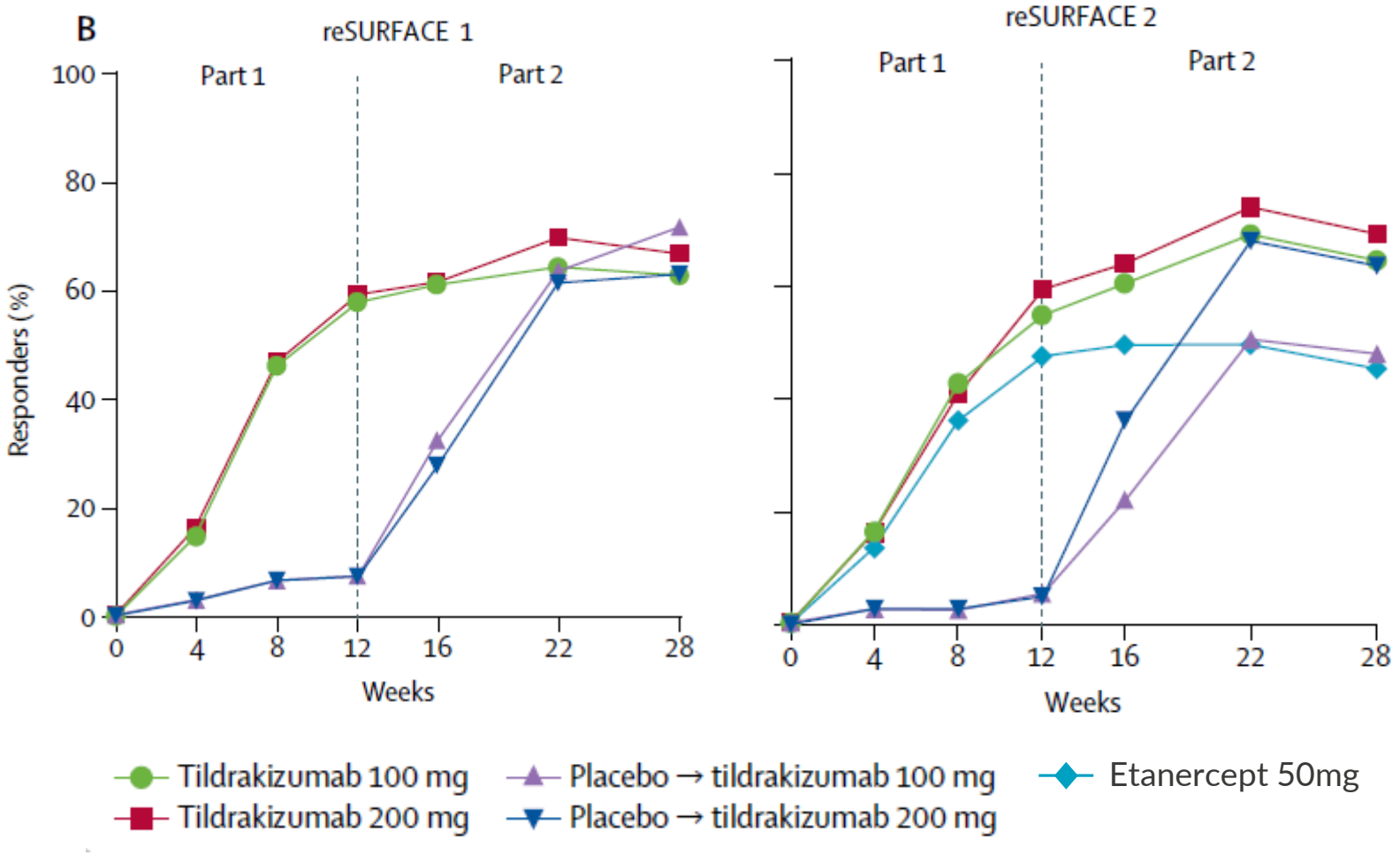
Full reSURFACE1 study design



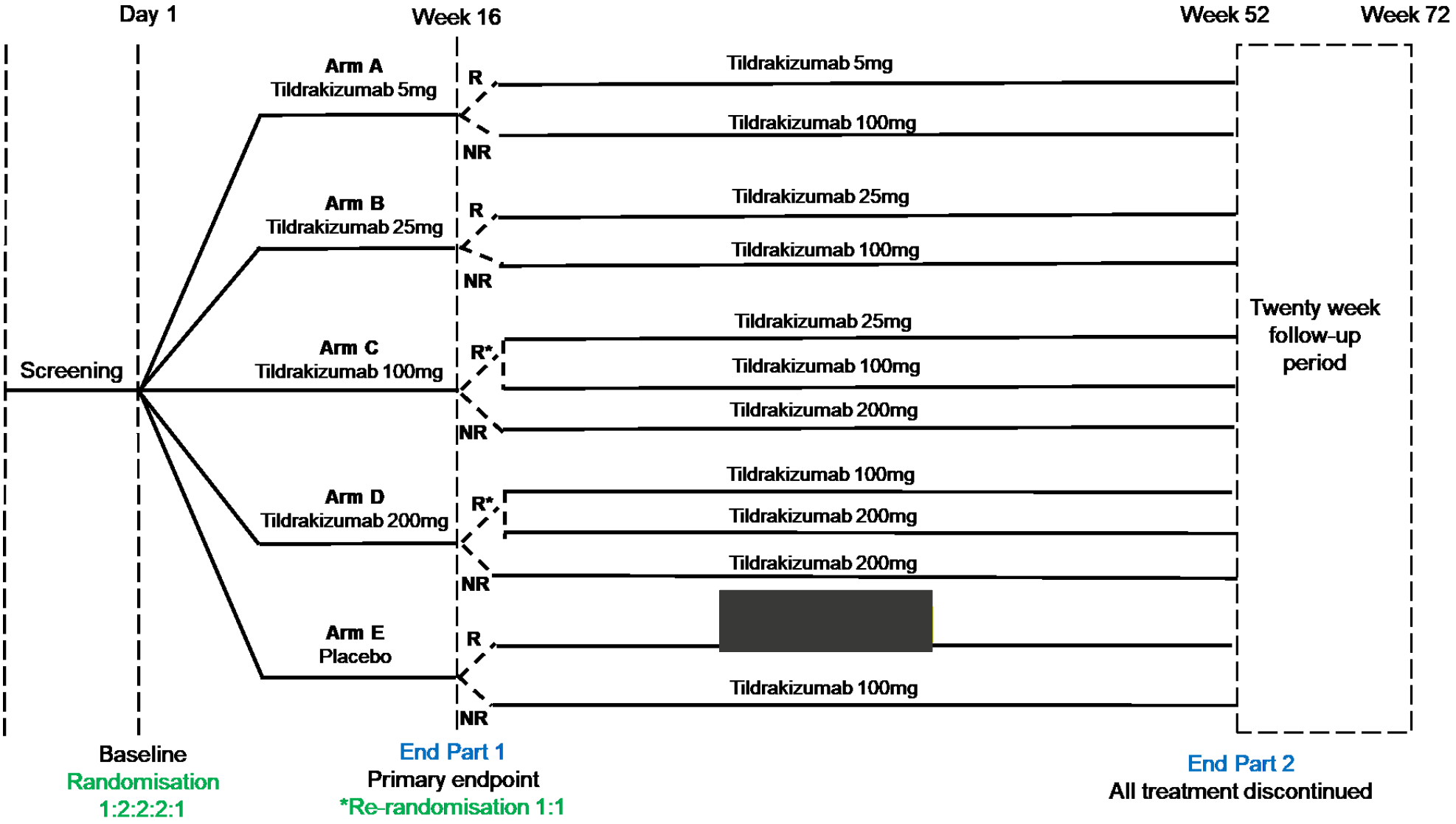
Full reSURFACE2 study design



Proportion of patients receiving PGA score 0/1



Full dose-finding study design (NCT01225731)



[redacted]

Dose-finding study baseline characteristics

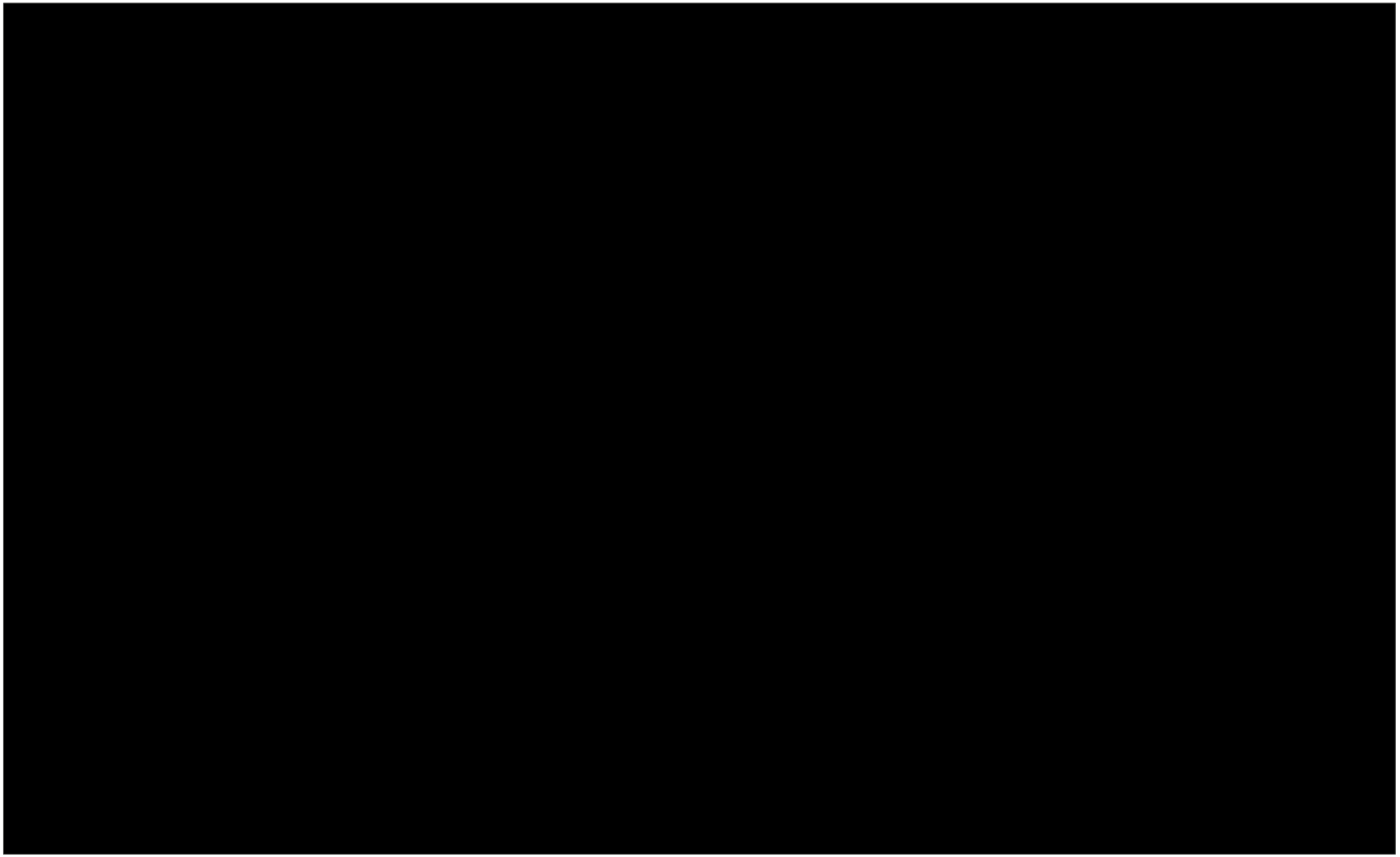
	Tildrakizumab 100mg (N=89)	Tildrakizumab 200mg (N=86)	Placebo (N=46)
Age (years), mean ± SD	45.5 ± 12.8	43.2 ± 12.6	45.9 ± 11.7
Male gender	76 (85)	65 (76)	38 (83)
Prior exposure to biologic therapy (PEBT)	15 (17)	19 (22)	13 (28)
≤90kg, PEBT: Yes	13 (15)	11 (13)	7 (15)
≤90kg, PEBT: No	44 (49)	42 (49)	21 (46)
>90kg, PEBT: Yes	10 (11)	11 (13)	6 (13)
>90kg, PEBT: No	22 (25)	22 (26)	12 (26)
Previous use of TNF inhibitor therapy	15 (17)	15 (17)	12 (26)
Baseline Psoriatic arthritis	15 (17)	15 (17)	11 (24)

Results for dose-finding study

Endpoint	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)

Network meta-analysis results – 200mg

Tildrakizumab 200mg at week 12/16, random effects model PASI 75 forest plot



Subgroup analysis – treatment dose

Subgroup analyses were performed to compare efficacy of treatment doses based on:

- Severity at baseline
- Weight

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tildrakizumab for treating moderate to severe plaque psoriasis [ID1060]

Document B
Company evidence submission

August 2018

File name	Version	Contains confidential information	Date
ID1060_Tildrakizumab_Document B Company Evidence Submission_10 Aug 18_ACIC	**Final**	**Yes**	**10 August 2018**

Contents

Tables

Figures

Abbreviations

Ab-NEG	Antibody-negative
Ab-POS	Antibody-positive
AD	Anxiety / depression
ADA	Adalimumab
ADAs	Anti-drug antibodies
A&E	Accident and Emergency
ASaT	All subjects as treated
ASR	All subjects randomised
BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic Interventions Register
BID	Twice daily
BIW	Twice weekly
BNF	British National Formulary
BRO	Brodalumab
BSA	Body surface area
BSC	Best supportive care
CHMP	Committee for Medicinal Products for Human Use
CMH	Cochrane-Mantel-Haenszel
CI	Confidence interval
CrI	Credible limits
CSR	Clinical study report
DERMBIO	Danish Biologic Interventions Registry
DIC	Deviance information criterion
DLQI	Dermatology Life Quality Index
DMF	Dimethyl fumarate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol five dimension scale
ERG	Evidence Review Group
ETA	Etanercept
FAS	Full analysis set
FE	Fixed effects
FTA	Fast track appraisal
GUS	Guselkumab

HCHS	Hospital and Community Health Service
HODaR	Health Outcomes Data Repository
HR	Hazard ratio
HRQoL	Health-related quality-of-life
ICER	Incremental cost-effectiveness ratio
INMB	Incremental net monetary benefit
ITT	Intention to treat
IXE	Ixekizumab
IBD	Inflammatory bowel disease
IL	Interleukin
kg	Kilogram
LOCF	Last observation carried forward
MACE	Major adverse cardiovascular events
MedDRA	Medical dictionary for regulatory activities
MI	Multiple Imputations
MIMS	Monthly Index of Medical Specialities
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NMSC	Non-malignant skin cancer;
NR	Non-responder
NRI	Non-responder imputation
NSAIDs	Non-steroidal anti-inflammatory drugs
OS	Overall survival
OWSA	One-way sensitivity analyses
PAS	Patient access scheme
PASI	Psoriasis Area and Severity Index
PASLU	Patient Access Scheme and Liaison Unit
PD	Pain / discomfort
PGA	Physician's Global Assessment
PICOS	Population Intervention Comparators Outcomes Study Design
PIIINP	N-Terminal propeptide of type III collagen
PP	Per protocol
PR	Partial responder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PSA	Probabilistic sensitivity analysis

PSS	Personal and social services
PSSRU	Personal Social Services Research Unit
PUVA	Psoralen ultraviolet A
QALY	Quality-adjusted life year
QoL	Quality-of-life
QW	Weekly
Q2W	Every two weeks
Q4W	Every four weeks
Q8W	Every eight weeks
Q12W	Every twelve weeks
R	Responder
RE	Random effects
RCT	Randomised controlled trial
sc	Subcutaneous
SD	Standard deviation
SE	Standard error
SEC	Secukinumab
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TA	Technology appraisal
TEAEs	Treatment emergent adverse events
TE-POS	Treatment emergent positive subjects
TIL	Tildrakizumab
TNF	Tumour necrosis factor
TRAE	Treatment-related adverse events
TSD	Technical Support Document
UK	United Kingdom
USA	United States of America
UST	Ustekinumab
UVA	Ultraviolet A
UVB	Ultraviolet B
Wk	Week

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate to severe plaque psoriasis.	The final indication for tildrakizumab has yet to be approved in Europe. It is anticipated that the indication for tildrakizumab will be: Adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.	Population anticipated to be the same as that in the indication specified in the European regulatory application.
Intervention	Tildrakizumab is a high-affinity *anti interleukin (IL)-23p19* monoclonal antibody that selectively blocks the p19 subunit of interleukin-23, which plays a key role in the development of psoriasis. Tildrakizumab is administered by subcutaneous injection.	As per the scope.	Not applicable.
Comparator(s)	If systemic non-biological treatment or phototherapy is suitable: • Systemic non-biological therapies (including methotrexate, ciclosporin and acitretin) • Phototherapy with or without psoralen If conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated: • 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) • Best supportive care	In clinical practice, tildrakizumab is expected to be used as an additional option alongside existing biologic treatment options. In line with this positioning the appropriate direct comparators are: • TNF-alpha inhibitors (etanercept, adalimumab) • IL-17 inhibitors (brodalumab, ixekizumab, secukinumab) • IL-23 inhibitor (guselkumab) • Interleukin IL-12/23 inhibitors (ustekinumab) • Best supportive care (for patients in whom biologic therapies are not tolerated or are contraindicated)	The target population for the tildrakizumab submission is patients for whom systemic biologic treatment is considered suitable. 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. They were included in the network-meta analysis within this submission because they permitted a more complete network with more connections between the comparators, with the objective of making the

			estimates of treatment effect more accurate. However on the basis that tildrakizumab is expected to be used as an additional option alongside existing biologic treatments, the economic analysis focuses on the biologics. Tildrakizumab will be licensed for moderate to severe psoriasis. 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.
Outcomes	The outcome measures to be considered include: • 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)	The outcome measures to be considered include: • severity of psoriasis • mortality • response rate • maintenance of response rate • adverse effects of treatment • health-related QoL	In order to ensure all health related benefits are captured, maintenance of response rate, considered to be the same as duration of response, has been included as a relevant outcome. Relapse rates were captured during off-treatment periods within the pivotal clinical studies. They are not therefore considered to be a relevant outcome to assess response to tildrakizumab 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.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. For the comparators, the availability and cost of biosimilars should be taken into account.	As per the scope. The cost effectiveness of treatments will be expressed in terms of incremental cost per QALY. The time horizon in the base case will be lifetime to enable the model to capture the full costs and benefits of treatment with tildrakizumab. Costs will be considered from an NHS and Personal Social Services Perspective.	
Subgroups to be considered	Where the evidence allows, the following subgroups will be considered: • Previous use of phototherapy and systemic non-biological therapy • Previous use of biological therapy • Severity of psoriasis (moderate, severe)	Data will be presented for the following subgroups: • Previous use of phototherapy and systemic non-biologic therapy • Previous use of biologic therapy • Severity of psoriasis (baseline PASI <20 and ≥20) • Body weight (baseline weight ≤90kg and >90kg)	The anticipated licensed dose of tildrakizumab is 100mg. However, in patients with certain characteristics (e.g. high disease burden, body weight ≥90kg), the 200mg dose may provide greater efficacy. The results of a pre-planned analysis of baseline body weight data and a post-hoc analysis of baseline severity data are therefore presented. Note: systemic non-biological therapy includes fumaric acid, methotrexate, methotrexate sodium, ciclosporin, acitretin, calcium monoethyl fumarate (+) dimethyl fumarate (+) magnesium monoethyl fumarate (+) zinc monoethyl fumarate, dimethyl fumarate and apremilast.

B.1.2 Description of the technology being appraised

The draft summary of product characteristics (SmPC) has been submitted, in confidence as part of the reference pack.[1] The European Public Assessment Report (EPAR) is not yet available but will be made available to NICE upon receipt.

Table 2: Technology being appraised

UK approved name and brand name	Approved name: Tildrakizumab Brand name: Ilumetri®▼
Mechanism of action	Tildrakizumab is a high-affinity anti IL-23p19 monoclonal antibody that selectively blocks the p19 subunit of interleukin-23. Through this mechanism of action tildrakizumab inhibits the release of pro-inflammatory cytokines and chemokines, which play a key role in the pathogenesis of psoriasis.[1]
Marketing authorisation / CE mark status	CHMP positive opinion received on 26 July 2018. Marketing authorisation anticipated: October 2018.
Indications and any restriction(s) as described in the SmPC	Proposed indication: For the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.
Method of administration and dosage	Tildrakizumab is administered by subcutaneous injection. The recommended dose in adults is 100mg at Weeks 0, 4 and every 12 weeks thereafter. In patients with certain characteristics (e.g. high disease burden, body weight ≥90kg) 200mg may provide greater efficacy. 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. Tildrakizumab is intended for use under the guidance and supervision of a clinician experienced in the diagnosis and treatment of psoriasis. After proper training in subcutaneous injection technique, patients may self-inject tildrakizumab if a clinician determines that it is appropriate. However, the clinician should ensure appropriate follow-up of the patient.
Additional tests or investigations	None required.
List price and average cost of a course of treatment	[redacted] for 1 x 100mg vial (single dose pack). Estimated annual cost = [redacted] for the first year (five doses) and [redacted] (4.33 doses) for subsequent years at list price. [redacted] for 2 x 100mg vial (single dose pack of 2 x 100mg). Estimated annual cost = [redacted] for the first year (five doses) and [redacted] (4.33 doses) for subsequent years at list price.
Patient access scheme (if applicable)	A simple discount patient access scheme (PAS) is anticipated providing a direct discount of [redacted] and a PAS submission has been made and is pending approval.

B.1.3 Health condition and position of the technology in the treatment pathway

Disease background

Psoriasis is a chronic, inflammatory, immune-mediated skin disease with an unpredictable course of flare-ups and remissions.[2,3] The prevalence of adult psoriasis in England and Wales is estimated to be 1.75%[4,5] which is approximately 838,000 people; plaque psoriasis accounts for up to 90%[6] of the cases of whom it is estimated 20% have moderate to severe psoriasis,[7] equating to 150,000 people. It has been estimated, however, that only 2.55%[5] of the population with plaque psoriasis are actually treated with biologics, equivalent to 21,000 patients.

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.[2,8] These lesions, which can be itchy and painful, can cause physical and emotional discomfort.[2,5,9]

Plaque psoriasis significantly affects physical, emotional and psychological well-being, may lead to substantial burden in terms of disability or psychosocial stigmatisation[10] and negatively affects quality-of-life (QoL).[2,8,9,11,12]

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.[8] Patients with moderate to severe disease have an increased risk of psoriatic arthritis, metabolic syndrome (including cardiovascular disease) and psychological disorders (anxiety, depression).[2,8,9] These co-morbid disorders can limit social interactions, impair school or work productivity and can eventually lead to suicidality[9,13,14] and an increased overall mortality risk.[2,8,9]

Current treatment options

There is no cure for psoriasis so ongoing long term management is required.[8,15]

Current clinical practice in England and Wales reflects the NICE pathway for psoriasis based on the NICE clinical guideline 153, Psoriasis: assessment and

management (October 2012) and recommendations from subsequent NICE technology appraisals (TAs) (Figure 1).[2,16]

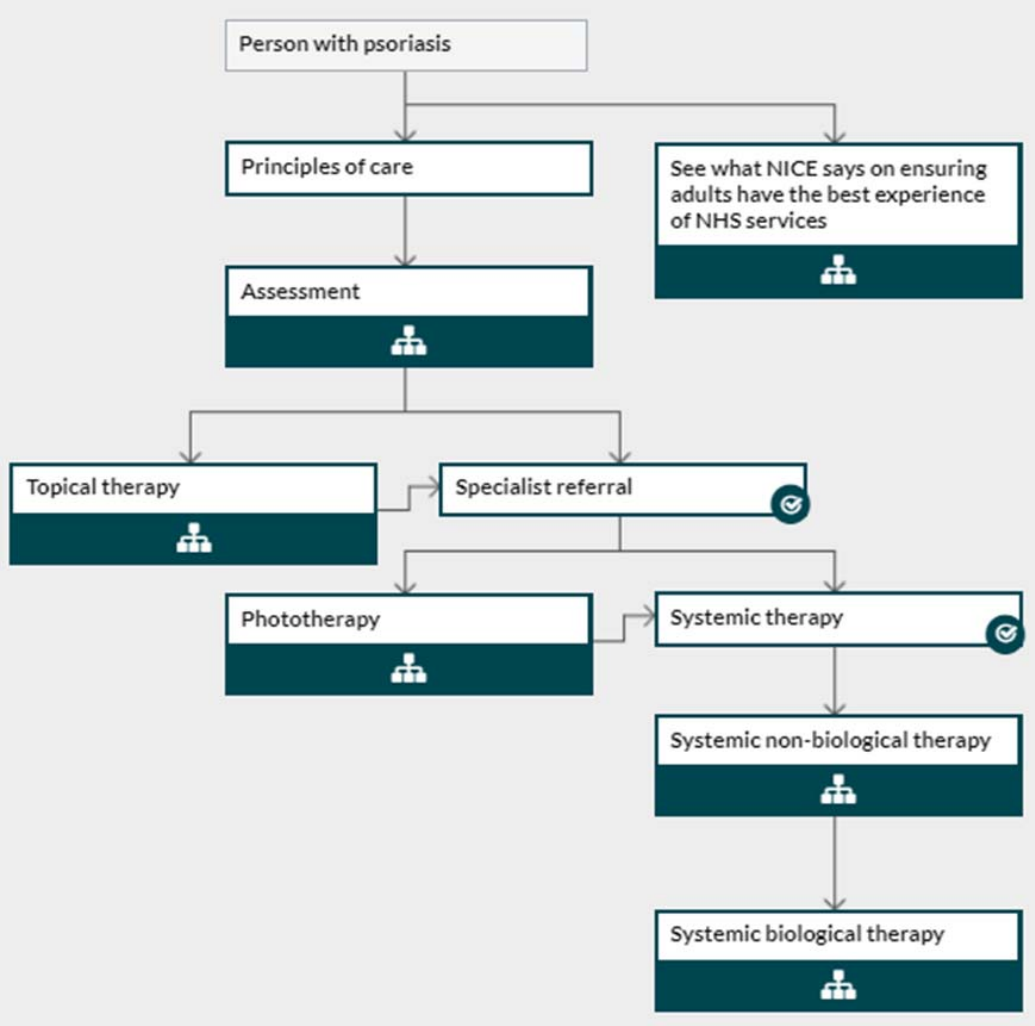
Treatment follows clinical need, with patients sequencing through therapies in the pathway.[16] Choice of treatment is based on severity of psoriasis (i.e. extent and locations of body surface affected, severity of redness, thickness and scaling of the skin, as well as its impact on patients QoL), and response to prior treatment (among other factors). It is tailored to the individual with consideration given to the patient's age, co-morbidities and current treatments, personal circumstances, preferences, as well as risks and benefits of available treatment options.[2,16]

There are three major forms of therapy:[15,16]

- topical therapy (e.g. vitamin D_3 analogues, corticosteroids);
- phototherapy (e.g. PUVA (psoralen plus ultraviolet (UV) A light) and
- systemic therapy, which includes
    - non-biological systemic therapy (conventional non-biologic treatments such as ciclosporin, methotrexate, acitretin, or further options dimethyl fumarate and apremilast) and
    - biological systemic therapy (adalimumab, brodalumab, etanercept, guselkumab, ixekizumab, secukinumab, ustekinumab, infliximab).

Moderate to severe plaque psoriasis generally requires systemic therapy. Commonly used first-line systemic therapies include non-biological therapies such as methotrexate and ciclosporin. However, individual responses vary and these treatments may not offer long term effectiveness or tolerability in all patients.[17] As such, patients may require biological therapies when there is an inadequate response or intolerance to non-biological therapy (Figure 1).[15]

Figure 1: NICE psoriasis pathway: overview



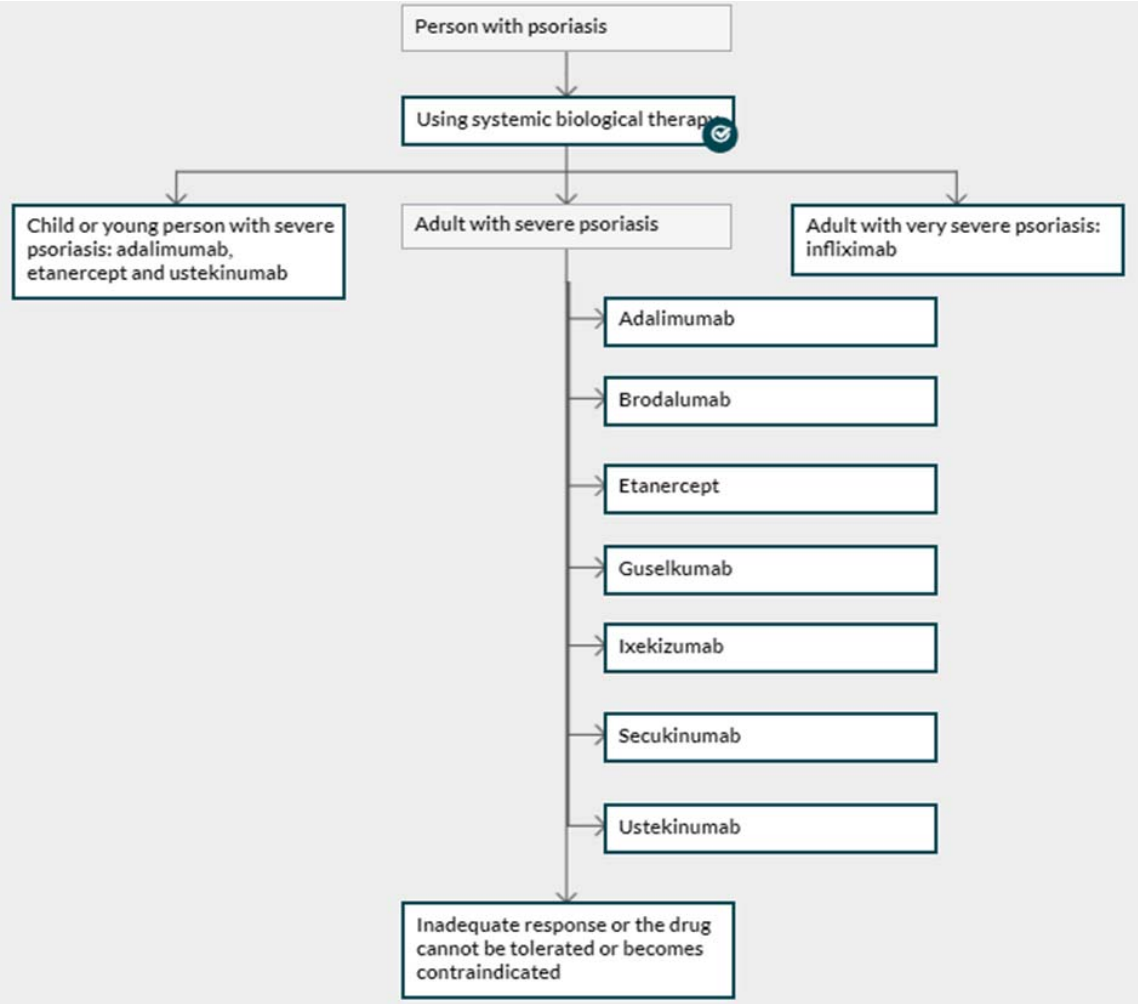
Source: NICE pathway for psoriasis 2017.[16]

Current biological therapy options

The NICE pathway[16] specifies the third-line use of biological therapies for adults with psoriasis who have not responded to, are intolerant to or are not eligible for standard systemic therapies or phototherapy.

For patients with psoriasis with PASI ≥10 and DLQI >10, biologic treatment options include: TNF-alpha inhibitors adalimumab (TA146) and etanercept (TA103); interleukin IL-12/23 inhibitor ustekinumab (TA180); interleukin IL-17A inhibitors secukinumab (TA350) and ixekizumab (TA442); interleukin IL-17 receptor inhibitor brodalumab (TA511) and the IL-23p19 inhibitor guselkumab (TA521). The TNF-alpha inhibitor infliximab (TA134) is recommended for very severe psoriasis (PASI ≥20, DLQI >18) (Figure 2).[18-25]

Figure 2: NICE psoriasis pathway: systemic biological therapy for psoriasis

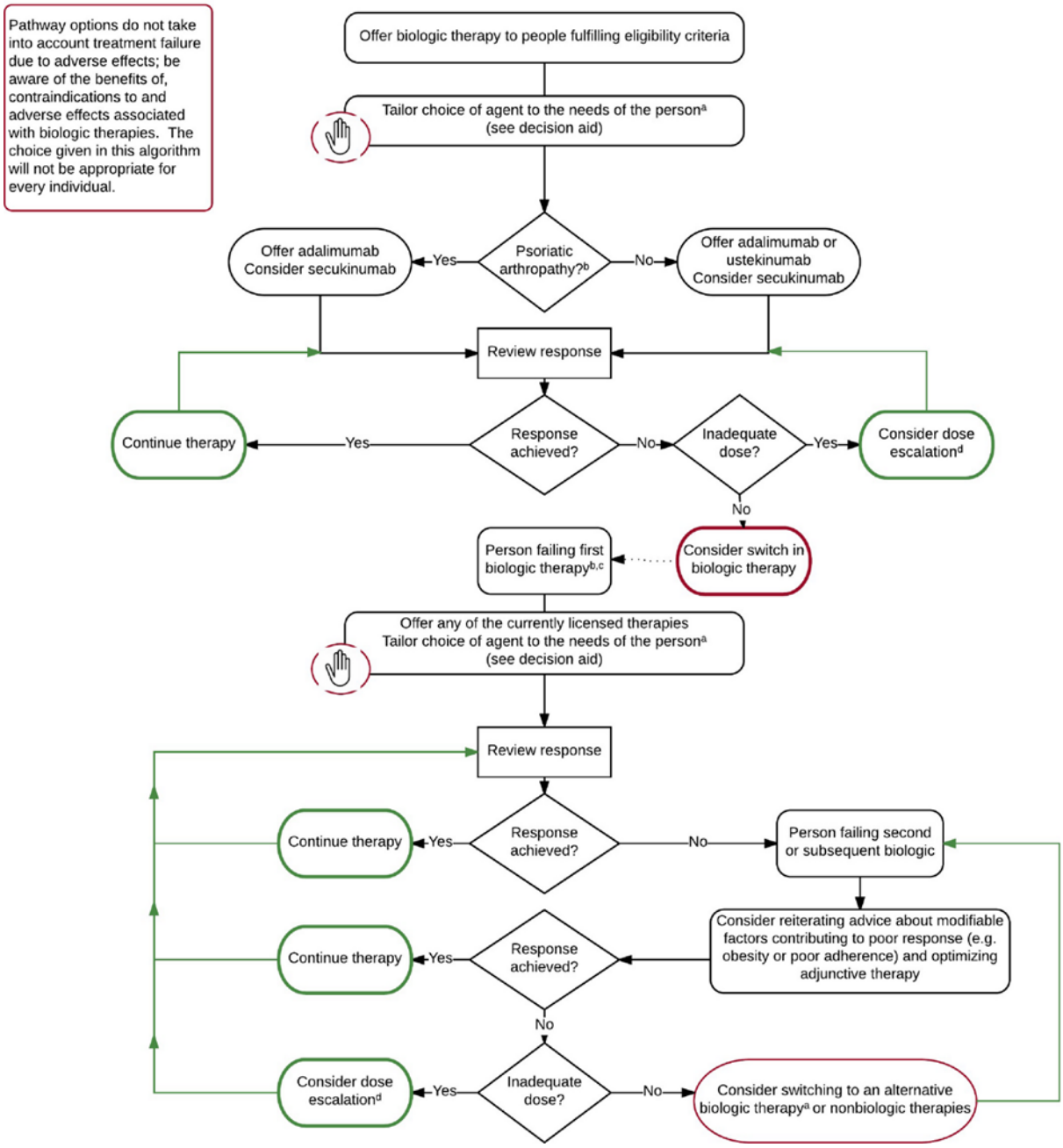


Source: NICE pathway for psoriasis 2017.[16]

The British Association of Dermatologists (BAD) has published UK-specific guidelines for biologic therapy for psoriasis, which recommend ustekinumab as a first-line biologic agent for adults with psoriasis who fulfil criteria for biologic therapy, adalimumab as a first-line biologic agent for adults with psoriasis particularly when psoriatic arthropathy is a consideration and secukinumab as a first-line biologic agent in adults with psoriasis, with or without psoriatic arthritis.[26] The BAD guidelines subsequently recommend that any of the currently licensed biologic therapies should be offered to patients when psoriasis has not responded to a first biologic therapy, although infliximab should be reserved for use in people with very severe disease or where other available biologic agents have failed or cannot be used (Figure 3).[26]

Current clinical practice in the UK in relation to the biologics reflects these guidelines whilst taking account of those medicines recommended following a NICE appraisal.[16]

Figure 3: British Association of Dermatologists pathway algorithm to guide choice of biologic therapy in adults with psoriasis



This guidance applies to biosimilars, subject to recommendations given within the British Association of Dermatologists position statement and European Medicines Agency guidelines. a) Take into account psoriasis factors (the goal of therapy e.g. PGA clear or nearly clear; disease phenotype and pattern of activity; disease severity and impact; presence of psoriatic arthritis; outcomes of previous treatment for psoriasis) and other factors (age; past or current comorbid conditions; conception plans; body weight). b) Take into account both psoriasis and psoriatic arthritis before initiating or making changes to biologic therapy, and manage treatment in consultation with a Rheumatologist; be aware that the presence of and phenotype of psoriatic arthritis (e.g. peripheral versus axial disease) may influence access to, choice of and dose of biologic therapy. c) Consider changing to an alternative biologic therapy if any of the following applies: the psoriasis does not achieve the minimum response criteria (primary failure) or the psoriasis initially responds but subsequently loses this response (secondary failure). d) Consider escalating the dose of biologic therapy in adults when an inadequate primary response may be due to insufficient drug dosing (e.g. in people who are obese or whose psoriasis relapses during the treatment cycle). Take into account that dose escalation may be associated with an increased risk of infection, and, depending on the drug, it may be off-licence and not funded. Currently, a dose-escalation strategy is not applicable to secukinumab or ixekizumab. Abbreviations: PGA: Physician Global Assessment. Source: Smith et al 2017.[26]

Issues with current biological treatment

Patients with moderate to severe plaque psoriasis continue to need well tolerated and effective lifelong therapy that is administered in a way and at a frequency that is convenient for their individual circumstances.[26-28]

The currently approved biologics for the treatment of psoriasis provide a range of treatment options. However, as biologic treatments target the immune system, it is important that they have minimal impact on the broader immune response, including the ability to fight infection, while maximising the disruptive effect on the inflammatory processes involved in psoriasis.

Although the available biologic agents are highly effective and show a favourable risk-benefit profile, differences in efficacy, side effects (which are dependent on the mechanism of action), dosing schedule, rapidity of action and maintenance of effect make the decision-making process around the most suitable therapy more complex for both patients and clinicians.[27]

Patient satisfaction, adherence to therapy and outcomes can vary based upon a patient's prior experience with treatments.[28] If a patient is dissatisfied with their current therapy, it can subsequently lead to poor compliance or treatment discontinuation.[27,29]

In addition a recent study investigating the differential survival associated with biologic therapies for the treatment of psoriasis highlighted a decrease in overall survival (OS) rate for biological therapies, with time with OS of 77% in the first year, 63% in the second year and of note, only 53% in the third year of therapy.[30] Common reasons for poor survival are lack of efficacy and adverse events.[29-31]

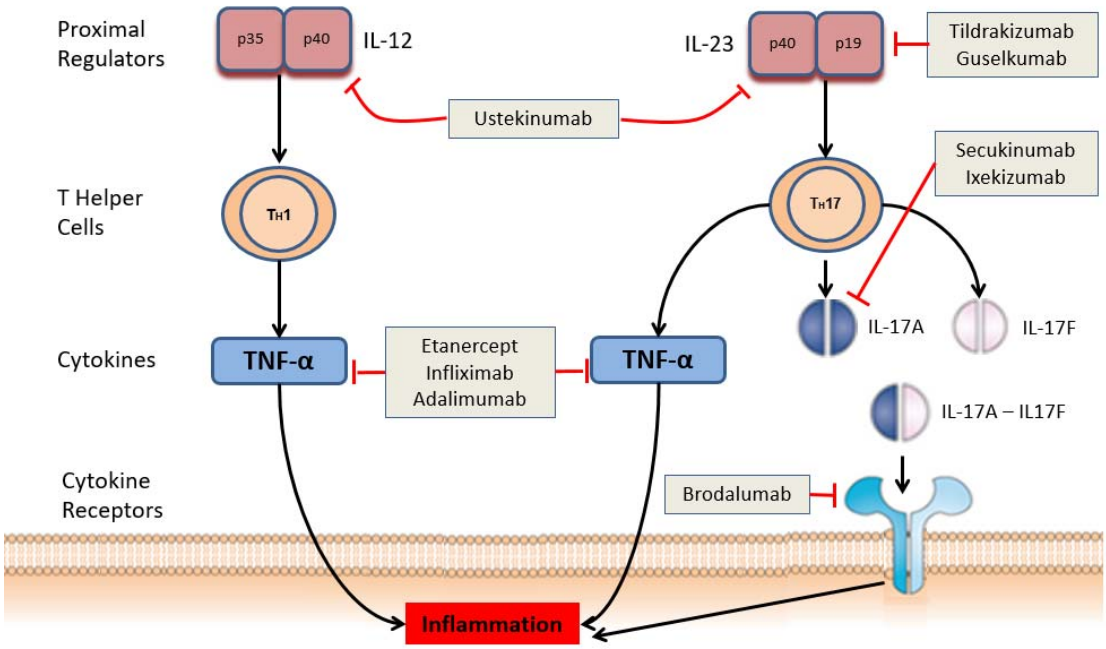
Switching therapies or increasing the frequency of dosing are common approaches used in an attempt to address inadequate outcomes.[28] However, there remains a significant unmet medical need for new therapies that offer therapeutic benefits in terms of the ability to select the appropriate dose for patients, maintenance of effect thereby reducing the costs and resources involved in switching therapy, as well as an attractive administration frequency, which offers convenience for patients.

Place of tildrakizumab in the treatment pathway

Tildrakizumab (also known as MK-3222 and SCH 900222) is a high affinity, humanised immunoglobulin antibody that specifically binds and neutralises human IL-23p19.[1]

Recent evidence suggests that IL-23 and the downstream Th17 pathway play a more important role in psoriasis than IL-12. Thus, selective inhibition of IL-23 is viewed as an improvement on targeting, compared to dual inhibition of both IL-12 and IL-23 (Figure 4).[32,33]

Figure 4: Place of biological therapies within the psoriasis autoimmune inflammatory pathway



Source: Adapted from Bartlett et al 2015.[33]

Tildrakizumab provides an alternative to existing biologic treatments, and has a mechanism of action specifically targeted to inhibit IL-23, a key regulatory cytokine in psoriasis.

In addition to proven efficacy and tolerability, tildrakizumab offers the benefits of a 12 weekly maintenance dosing schedule via subcutaneous injection which may be considered a convenient alternative to more frequent dosing regimens of current

biologics for patients requiring lifelong therapy. There is also the option to self-administer tildrakizumab after appropriate training. Tildrakizumab will increase the range of options available for patients requiring biological treatment for chronic plaque psoriasis and should be positioned in the treatment pathway along with the other biologic treatment options in Figure 2.

B.1.4 Equality considerations

None.

B.2 Clinical efficacy

B.2.1 Identification and selection of relevant studies

Appendix D includes full details of the process and methods used during a systematic literature review (SLR), in line with NICE submission requirements,[34] to identify and select all relevant clinical evidence relating to the use of tildrakizumab for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.

The PICOS criteria are summarised in Table 3. Details of the full search strategy and search results are shown in Appendix D.

Table 3: Summary of systematic review eligibility criteria

	Inclusion Criteria	**Exclusion Criteria**
Population	Adult patients (≥18 years of age) with moderate to severe chronic plaque psoriasis	Children younger than 18 years
Intervention	Tildrakizumab (100mg or 200mg)	
Comparators	Ustekinumab (Stelara, CNTO 1275) Guselkumab (Tremfya) Secukinumab (Cosentyx, AIN457) Etanercept (Enbrel) Adalimumab (Humira, Exemptia) Brodalumab (Siliq, Kyntheum) Ixekizumab (Taltz) Risankizumab Apremilast (Otezla) Dimethyl fumarate (Skilarence) Placebo Best supportive care (BSC)	
Outcomes	Severity of psoriasis: • Psoriasis Area Severity Index (PASI) 50, 75, 90 or 100 • Physicians / Investigators global assessment (P / IGA)	

	• Data will be collected at all available time points DLQI Psoriasis symptom inventory Mortality Response rate Adverse effects of treatment Withdrawals due to adverse effects HRQoL	
Study design	Effects: • RCTs • Cross over trials with data at cross over • Non-randomised controlled trials Safety: • Cohort studies • Case control studies • Cross sectional studies • Case series studies	Case studies Case reports
Limits	English language only Any dates	Non-English language publications

The review was conducted for use on a global basis and so includes a broader base of comparators than was required for this submission.

Search strategy

The search strategy, which was designed to identify studies of the effects, safety and cost-effectiveness of tildrakizumab, comprises one concept: tildrakizumab.

Details of the full search strategy and search results are shown in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The review identified three relevant studies (reported in 12 documents as outlined in Appendix D): one Phase IIb dose-finding study[35] and two Phase III comparator studies (reSURFACE 1 and reSURFACE 2).[36-38]

Phase IIb study

Table 4: Clinical effectiveness evidence: Phase IIb study

Study	NCT01225731[35]
Study design	Phase IIb randomised, double-blind dose-finding study.
Population	355 adults with chronic plaque psoriasis (≥6 months), who were candidates for phototherapy or systemic therapy; had a PASI score ≥12; psoriasis body surface area involvement (BSA) ≥10%; and a PGA of moderate, marked or severe at baseline.
Intervention(s)	Tildrakizumab 5mg, 25mg, 100mg or 200mg.
Comparator(s)	Placebo.

Indicate if trial supports application for marketing authorisation	Yes	√	**Indicate if trial used in the economic model**	Yes	√
	No			No	
Rationale for use / non-use in the model	As this study is a dose finding study, the clinical data are not included in the clinical efficacy sections. However, the clinical data relevant to submitted doses, feeds into the NMA and hence the economic model. The safety results from this study are included in pooled safety analyses along with the safety data from the Phase III studies (reported in section B.2.10).				
Reported outcomes specified in the decision problem	**Primary endpoints:** 1. The proportion of participants achieving at least 75% improvement in the PASI (PASI 75), at Week 16. **Secondary endpoints:** 1. PASI 75 response at Week 12. 2. The proportion of participants with a PGA status of 'cleared' or 'minimal' at Week 16. 3. The proportion of participants achieving a ≥90% reduction in PASI score (PASI 90) at Week 16. 4. Other secondary endpoints include time to PASI 75 and the mean change from baseline in the Dermatology Life Quality Index (DLQI) at Week 16.				
All other reported outcomes	See Papp et al 2015.[35]				

Phase III studies

The main evidence on the efficacy and safety of tildrakizumab in moderate to severe plaque psoriasis is available from two pivotal Phase III studies: reSURFACE 1 and reSURFACE 2.[36-38]

These studies investigated the efficacy and safety of tildrakizumab 100mg and 200mg in the treatment of adult patients with moderate to severe chronic plaque psoriasis[36] and provided the clinical effectiveness evidence included in this submission.

The anticipated European licensed dose of tildrakizumab will be 100mg. However, the licence will also include that in patients with certain characteristics (e.g. high disease burden, body weight ≥90kg) the 200mg dose may provide greater efficacy; so data for tildrakizumab 200mg from both reSURFACE studies are presented along with the 100mg data.

In addition, section B.2.7 provides data pertaining to certain patient subgroups where the 200mg dose of tildrakizumab may provide greater efficacy.

Table 5: Clinical effectiveness evidence: reSURFACE 1

Study	Trial P010 (NCT01722331) also known as reSURFACE 1: Reich et al 2017[36,37]				
Study design	International three-part Phase III randomised, double-blind, placebo-controlled, parallel-group, multicentre study.				
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.				
Intervention(s)	Tildrakizumab 100mg, tildrakizumab 200mg.				
Comparator(s)	Placebo.				
Indicate if trial supports application for marketing authorisation	Yes	√	**Indicate if trial used in the economic model**	Yes	√
	No			No	
Rationale for use / non-use in the model	Pivotal clinical study supporting European marketing authorisation application for tildrakizumab.				
Reported outcomes specified in the decision problem	**Co-primary endpoints:** 1. The proportion of participants achieving at PASI 75 response at Week 12. 2. 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 endpoints:** 1. Protocol-defined key secondary endpoints were PASI 90 and PASI 100 response at Week 12. 2. 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. **In addition to using the primary endpoint of the proportion of patients achieving a PASI 75 response at Week 12, the economic model uses PASI 50 and 90 at week 12 as well as the proportion of patients achieving a PASI 50, 75 and 90 response at Week 28 in a scenario analysis. The model also uses EQ-5D data from the trial which were collected for exploratory analyses.**				
All other reported outcomes	See Table 7.				

Source: Reich et al 2017.[36]

Table 6: Clinical effectiveness evidence: reSURFACE 2

Study	Trial P011 (NCT01729754) also known as reSURFACE 2: Reich et al 2017[36,38]				
Study design	International three-part Phase III randomised, double-blind, placebo-controlled, parallel-group, multicentre study.				
Population	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 and etanercept 50mg.				
Indicate if trial supports application for marketing authorisation	Yes	√	**Indicate if trial used in the economic model**	Yes	√
	No			No	
Rationale for use / non-use in the model	Pivotal clinical study supporting European marketing authorisation application for tildrakizumab.				
Reported outcomes specified in the decision problem	**Co-primary endpoints:** 1. The proportion of participants achieving a PASI 75 response at Week 12. 2. 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 endpoints:** 1. Protocol-defined key secondary endpoints were PASI 90 and PASI 100 response at Week 12 and PASI 75 and PGA response at Week 28. 2. 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. **In addition to using the primary endpoint of the proportion of patients achieving a PASI 75 response at Week 12, the economic model uses PASI 50 and 90 at week 12 as well as the proportion of patients achieving a PASI 50, 75 and 90 response at Week 28.**				
All other reported outcomes	See Table 7.				

Source: Reich et al 2017.[36]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

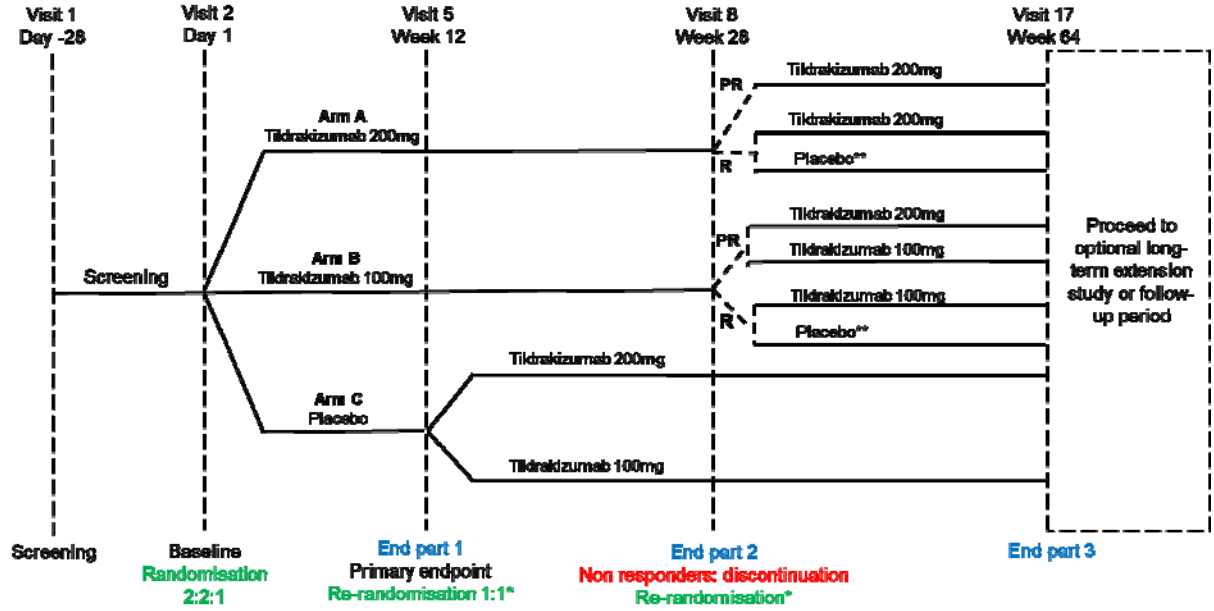
Information on the trial design for reSURFACE 1 and reSURFACE 2 is provided below in Figure 5 and Figure 6, respectively, with comparative summaries of trial methodology provided in Table 7.

Trial design

reSURFACE 1[36,37]

Figure 5 illustrates the study design for reSURFACE 1. The details of treatment assignment for each part of the study are included in Table 7.

Figure 5: reSURFACE 1 study design

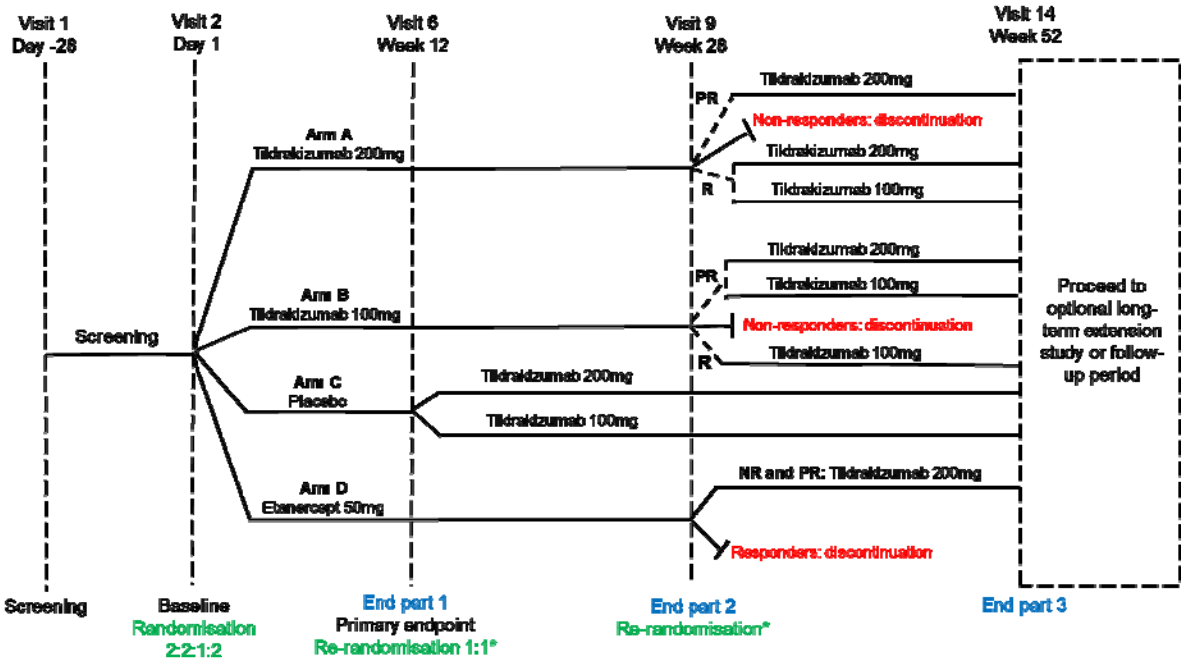


Non-responders (NR: who achieved <50% improvement in PASI response from baseline) were discontinued at Week 28. Partial responders (PR) were subjects who achieved ≥50% but <75% improvement in PASI response from baseline. Responders (R) were subjects who achieved ≥75% improvement in PASI response from baseline. * Participants in the placebo group (Arm C) were re-randomised (1:1) at Week 12 to receive either tildrakizumab 200mg or 100mg; participants in the tildrakizumab 100mg and 200mg groups were re-randomised at Week 28 depending on whether they had a response or partial response to treatment. ** Participants in Arms A and B who relapsed on placebo between Week 28 and Week 64 were re-initiated on their initial treatment with tildrakizumab (100mg or 200mg). Adapted from Reich et al 2017.[36]

reSURFACE 2[36,38]

Figure 6 illustrates the trial design for reSURFACE 2. The details of treatment assignment for each part of the study are included in Table 7.

Figure 6: reSURFACE 2 study design



NRs were subjects who achieved <50% improvement in PASI response from baseline. PR were subjects who achieved ≥50% but <75% improvement in PASI response from baseline. R were subjects who achieved ≥75% improvement in PASI response from baseline. In Arms A and B, NRs were discontinued at Week 28, whereas in Arm D, Rs were discontinued at Week 28 *Participants in the placebo group (Arm C) were re-randomised (1:1) at Week 12 to receive either tildrakizumab 200mg or 100mg; participants in the tildrakizumab 200mg group (Arm A) and 100mg group (Arm B) were re-randomised at Week 28 depending on whether they had a response or partial response to treatment. In Arm D, there was a 4-week washout period in NR and PR patients on etanercept before they started tildrakizumab 200mg. Abbreviations: NR: non responders; R: responders. Adapted from Reich et al 2017.[36]

Comparative summary of trial methodology

Table 7: Comparative summary of trial methodology for the reSURFACE 1 and reSURFACE 2 studies

	reSURFACE 1 study (P010)	reSURFACE 2 study (P011)
Location	118 sites in Australia, Canada, Japan, the UK and the USA.	132 sites in Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, Israel, Netherlands, Poland and the USA.
Trial design	Both studies were international, three-part, Phase III, double-blind, randomised, placebo-controlled, parallel-group, multicentre studies. The reSURFACE 1 study was of 64 weeks duration (see Figure 5) and was carried out between 10 December 2012 and 28 October 2015. The reSURFACE 2 study was of 52 weeks duration (see Figure 6) and was carried out between 12 February 2013 and 28 September 2015. Randomisation was carried out using computer-generated randomisation sequences along with an interactive voice-response system and interactive web-response system to allocate participants to groups. Randomised treatment assignments on Day 1 were done by region (e.g. North America, European Union and Japan) and stratified for bodyweight (≤90kg or >90kg) and previous exposure to biological therapy for psoriasis. Participants in Japan were also stratified for psoriatic arthritis at baseline. A maximum of 40% of randomised participants were permitted to have had previous exposure to biologics. A maximum of 30% of randomised participants were permitted to have a diagnosis of psoriatic arthritis at baseline. Re-randomisation assignments at Weeks 12 and 28 were also done by region and stratified by bodyweight (≤90kg or >90kg). In both the reSURFACE studies, investigators, participants and study personnel were blinded to group allocation and remained blinded until completion of the base study (Week 64 in reSURFACE 1 and Week 52 in reSURFACE 2). The team conducting the analysis was blinded until the database was locked.	
Eligibility criteria for participants	• ≥18 years of age, of either sex and of any race / ethnicity. • 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). • PGA of at least moderate disease (≥3) at baseline (Visit 2). Full inclusion and exclusion criteria are detailed in the supplementary appendix to the Reich et al publication.[36] All inclusion and exclusion criteria were identical for the re-SURFACE 1 and reSURFACE 2 studies, with the addition of two exclusion criteria in the reSURFACE 2 study: exclusion of patients who had previously used etanercept and patients with latex allergy.	
Settings and locations where the data were collected	Hospital dermatology units, specialty clinics, private practices and research sites.	

<table>
<tr><td>Trial drugs</td><td colspan="2">Subjects received tildrakizumab subcutaneously (sc) at the dose level and frequency described below. To maintain blinding, a matching tildrakizumab placebo was provided and administered by sc injection. In the reSURFACE 2 study, etanercept and etanercept placebo were also administered by sc injection.</td></tr>
<tr><td></td><td>Part 1: Weeks 0 to 12, Visits 2 to 5
Participants were randomly assigned (2:2:1) to receive:
• Arm A (N=308): Tildrakizumab 200mg at baseline (Week 0) and Week 4.
• Arm B (N=309): Tildrakizumab 100mg at baseline (Week 0) and Week 4.
• Arm C (N=155): Placebo at baseline (Week 0) and Week 4.

Part 2: Weeks 12 to 28, Visits 6 to 8
• Arm A: Matching tildrakizumab placebo at Week 12, followed by tildrakizumab 200mg at Week 16.
• Arm B: Matching tildrakizumab placebo at Week 12, followed tildrakizumab 100mg at Week 16.
• Arm C: Re-randomised at Week 12 (1:1) to receive either first dose of tildrakizumab 200mg or tildrakizumab 100mg, followed by an additional dose of the study medication according to their re-randomised treatment assignment at Week 16.

Part 3: Weeks 28 to 64, Visits 9 to 17
At Week 28, all enrolled subjects were assessed for improvement in PASI score from baseline. Subjects with <PASI 50 response (non-responders) were discontinued from the study, irrespective of treatment arm. This was pre-specified for non-responders in Arms A and B but protocol amendment 1 (010-01) also allowed non-responders from Arm C to be discontinued at Week 28 in order to maintain blinding.
• Arm A: Subjects with ≥PASI 50 but <PASI 75 response (partial responders) continued with current treatment, tildrakizumab 200mg, every 12 weeks until Week 64. Subjects with ≥PASI 75 response (responders) were re-randomised in a 1:1 ratio to either continue on their initial therapy (tildrakizumab 200mg every 12 weeks) until Week 64 or to receive placebo at Week 28. Subjects who were re-randomised to placebo received placebo every 4 weeks until relapse (reduction in maximum PASI response by 50%), when</td><td>Part 1: Weeks 0 to 12, Visits 2 to 6
Participants were randomly assigned (2:2:1:2) to receive:
• Arm A (N=314): Tildrakizumab 200mg at baseline (Week 0) and Week 4 and etanercept placebo twice weekly.
• Arm B (N=307): Tildrakizumab 100mg at baseline (Week 0) and Week 4 and etanercept placebo twice weekly.
• Arm C (N=313): Tildrakizumab placebo at baseline (Week 0) and Week 4 and etanercept placebo twice weekly.
• Arm D (N=156): Etanercept 50mg twice per week and tildrakizumab placebo at baseline (Week 0) and Week 4.

Part 2: Weeks 12 to 28, Visits 7 to 9
• Arm A: Matching tildrakizumab placebo at Week 12, followed by tildrakizumab 200mg at Week 16. Etanercept placebo was given weekly.
• Arm B: Matching tildrakizumab placebo at Week 12, followed by tildrakizumab 100mg at Week 16. Etanercept placebo was given weekly.
• Arm C: Re-randomised at Week 12 (1:1) to receive first dose of tildrakizumab 200mg or tildrakizumab 100mg, followed by an additional dose of the study medication according to their re-randomised treatment assignment at Week 16. Etanercept placebo was given weekly.
• Arm D: Etanercept 50mg once per week and tildrakizumab placebo at Week 12 and Week 16.

Part 3: Weeks 28 to 52, Visits 10 to 14
At Week 28, subjects from Arm A (tildrakizumab 200mg), Arm B (tildrakizumab 100mg) and Arm D (etanercept) were re-randomised based on their PASI responder status.
• Arm A: At Week 28, non-responders were discontinued from the study. Responders were re-randomised in a 1:1 ratio to either continue tildrakizumab 200mg or receive tildrakizumab 100mg every 12 weeks until Week 52. Partial responders continued to receive tildrakizumab 200mg</td></tr>
</table>

	subjects were re-treated with tildrakizumab 200mg. Subsequent dosing occurred after 4 weeks of treatment re-initiation and every 12 weeks thereafter until Week 64. • **Arm B**: Partial responders were re-randomised in a 1:1 ratio to receive tildrakizumab 100mg or tildrakizumab 200mg every 12 weeks until Week 64. Responders were re-randomised in a 1:1 ratio to either continue on their initial therapy (tildrakizumab 100mg every 12 weeks) until Week 64 or to receive placebo at Week 28. Subjects who were re-randomised to placebo received placebo every 4 weeks until relapse, when subjects were re-treated with tildrakizumab 100mg. Subsequent dosing occurred after 4 weeks of treatment re-initiation and every 12 weeks thereafter until Week 64. • **Arm C**: Responders and partial responders continued to receive tildrakizumab 200mg or 100mg every 12 weeks according to their re-randomised treatment assignment at Week 12 until Week 64.	every 12 weeks until Week 52. Tildrakizumab placebo was given at Weeks 32, 36 and 48. • **Arm B**: At Week 28, non-responders were discontinued from the study. Responders continued to receive tildrakizumab 100mg every 12 weeks until Week 52. Partial responders were re-randomised in a 1:1 ratio to either continue tildrakizumab 100mg or receive tildrakizumab 200mg every 12 weeks until Week 52. Tildrakizumab placebo was given at Weeks 32, 36 and 48. • **Arm C**: Responders and partial responders continued to receive tildrakizumab 200mg or 100mg every 12 weeks until Week 52, according to their re-randomised treatment assignment at Week 12. Tildrakizumab placebo was given at Weeks 32, 36 and 48. • **Arm D**: At Week 28, etanercept responders were discontinued from the study. Partial responders and non-responders were switched to tildrakizumab 200mg after a 4-week washout period and received doses at Weeks 32, 36 and 48. Tildrakizumab placebo was given at Weeks 28, 40 and 52.
	Long term open label safety extension study At the end of the study period (Week 64 in reSURFACE 1 and Week 52 in reSURFACE 2), subjects were permitted to proceed to an optional long term open label safety extension study (lasting 192 weeks) or to the reSURFACE study follow-up period (20 weeks). The primary objective of the long term extension study was to assess the long term safety / tolerability of tildrakizumab in subjects with moderate to severe chronic plaque psoriasis.	
Permitted and disallowed concomitant medication	During the entire study, subjects should have used only study-approved concomitant medications, but, according to the judgement of the investigator, additional therapies may have been permitted for safety reasons. **Prohibited concomitant medication after randomisation and throughout the studies** • Topical psoriasis treatment including any class of topical corticosteroid. • Conventional systemic psoriasis therapy (e.g. ciclosporin, methotrexate, acitretin, fumaric acid esters) or phototherapy (e.g. UVB light phototherapy, Psoralen-UVA (PUVA) therapy, tanning salon or home-administered UVB). • Treatment with injectable or oral corticosteroids. • Treatment with a biological agent other than study medication (including monoclonal antibodies, alefacept). • Treatment with investigational agent (other than study medication). **Permitted concomitant medication after randomisation and throughout the studies** The use of any concomitant medication must relate to the documented medical history, prophylaxis or an adverse event of the subject. The following treatments were permitted during the study:	

<table>
<tr><td></td><td colspan="2">

Acetaminophen (paracetamol) or aspirin.
Medications needed to treat pre-existing medical conditions that are not exclusionary to the trial.
Medications necessary to treat adverse events or medical emergencies.
Bland emollients (without α or β-hydroxy acids or keratolytics).
Medicated shampoos that do not contain corticosteroids.
Vitamins, supplements, antacids and other over the counter medications that are not exclusionary to the trial.

In addition, in the reSURFACE 1 study, the 32 subjects randomised at Japanese investigative sites with psoriatic arthritis at baseline were allowed concurrent treatment with stable doses (minimum of four weeks prior to the first dose of study medication) of NSAIDs to week 12 after which the NSAID dose could be titrated or initiated if necessary, per investigator's discretion.
The medications, supplements and other substances prohibited prior to randomisation are listed within the exclusion criteria in the supplementary appendix to the Reich et al publication.[36]
</td></tr>
<tr><td rowspan="3">Primary, secondary and safety endpoints</td><td colspan="2">Details of the pre-specified primary efficacy and key secondary efficacy endpoints and the safety endpoints are provided below. Details of all other endpoints including secondary efficacy, exploratory and all safety endpoints are included in the supplementary appendix to the Reich et al publication.[36]
The outcomes used in the economic model are in bold and italics.</td></tr>
<tr><td colspan="2">Co-primary efficacy endpoints

Proportion of subjects with a PASI 75 response at Week 12 (included in the economic model).
Proportion of subjects with a PGA score of ‘clear’ or ‘minimal’, with at least a two-grade reduction from baseline, at Week 12.
</td></tr>
<tr><td>Key secondary efficacy endpoints
Proportion of subjects with PASI 90 response at Week 12.
Proportion of subjects with PASI 100 response at Week 12 (protocol amendment 7 to change from other secondary endpoint to a key secondary endpoint).

In addition the proportion of subjects with PASI 75 response at Week 28 was included in the economic model.</td><td>Key secondary efficacy endpoints
Proportion of subjects with PASI 90 response at Week 12.
Proportion of subjects with PASI 100 response at Week 12 (protocol amendment 4 to change from other secondary endpoint to a key secondary endpoint).
Proportion of subjects with PASI 75 response at Week 28 was included in the economic model
Proportion of subjects achieving a PGA score of ‘clear’ or ‘minimal’, with at least a two-grade reduction from baseline, at Week 28.</td></tr>
<tr><td></td><td colspan="2">Safety endpoints
The pre-specified safety endpoints are related to the primary study objectives.
The analysis of safety / tolerability data followed a tiered approach. Adverse experiences of special interest that were identified a priori constitute ‘Tier 1’ safety / tolerability endpoints. Commonly occurring adverse events (AEs) (defined as at least four subjects in any treatment group) were considered as Tier 2. In addition, certain pre-specified safety / tolerability endpoints were considered Tier 2 regardless of the number of subjects in any treatment group. Any other adverse event preferred terms, plus laboratory assessments not analysed in Tier 1 and Tier 2, constitute descriptive safety / tolerability endpoints (Tier 3).
Information relevant to the appraisal is included in this table. Additional information if required is available in the supplementary appendix to Reich et al.[36]</td></tr>
</table>

Other outcomes used in the economic model / specified in the scope	EQ-5D data collected at all time points up to Week 64 were utilised in an exploratory analysis and are included in the economic model.	EQ-5D data were not collected so no additional data from this study were used in the economic model.
Pre-planned subgroups	Primary endpoints at Week 12 were evaluated separately in the following subgroups: • Body weight (≤90kg, >90kg). • Prior exposure to biologic therapy for psoriasis (Yes / No). For each subgroup, treatment differences with 95% confidence interval (CI) comparing each dose of tildrakizumab with placebo were provided. In addition, treatment effect consistency across the following subgroups was assessed descriptively via summary statistics for the primary endpoints: • Age (<65 / ≥65 years). • Gender. • Race. • Region. • TNF antagonist response among subjects previously treated for psoriasis (Yes / No). • Psoriatic arthritis (Yes / No). • Failure of at least one traditional systemic therapy (methotrexate, ciclosporin, phototherapy) (Yes / No).	Efficacy in the primary and key secondary endpoints at Week 12 were evaluated separately in the following subgroups: • Body weight (≤90kg, >90kg). • Prior exposure to biologic therapy for psoriasis (Yes / No). • Failure of at least one traditional systemic therapy (methotrexate, ciclosporin, phototherapy) (Yes / No). For each subgroup, treatment differences with 95% CI comparing each dose of tildrakizumab with placebo were provided. In addition, treatment effect consistency across the following subgroups was assessed descriptively via summary statistics for the primary and key secondary endpoints: • Age (<65 / ≥65 years). • Gender. • Race. • Region. • TNF antagonist response among subjects previously treated for psoriasis (Yes / No). • Psoriatic arthritis (Yes / No).
	Details of post-hoc analyses (severity of psoriasis according to PASI ≥20 and PASI <20 and previous use of phototherapy and systemic non-biologic therapy) are discussed in section B.2.7 and Appendix E. Subgroup data for severity of psoriasis and body weight were included in the economic model as scenario analyses as these criteria may impact the choice of treatment dose.	

Abbreviations: BSA: Body Surface Area; CI: Confidence Interval; kg: kilograms; NSAIDS: non-steroidal anti-inflammatory agents; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; PUVA: psoralen combined with ultraviolet A; sc: subcutaneously; UK: United Kingdom; USA: United States of America; UV: ultraviolet.
Source: Reich et al 2017 and reSURFACE 1 and reSURFACE 2 clinical study reports (CSRs).[36-38]

Baseline characteristics of subjects across treatment groups

Demographic variables, baseline characteristics, primary and secondary diagnoses, cardiovascular risk factors and prior and concomitant therapies are summarised in Table 8 by treatment in all subjects as randomised (ASR) populations for the reSURFACE 1 and reSURFACE 2 studies. Baseline demographic characteristics were similar in all treatment groups within each study.

Table 8: Baseline characteristics of subjects in reSURFACE 1 and reSURFACE 2 across treatment groups

	reSURFACE 1			reSURFACE 2			
	Tildrakizumab 100mg (N=309)	**Tildrakizumab 200mg (N=308)**	**Placebo (N=155)**	**Tildrakizumab 100mg (N=307)**	**Tildrakizumab 200mg (N=314)**	**Etanercept 50mg (N=313)**	**Placebo (N=156)**
Male	207 (67%)	226 (73%)	100 (65%)	220 (72%)	225 (72%)	222 (71%)	112 (72%)
Age (years)	46.4 (13.1)	46.9 (13.2)	47.9 (13.5)	44.6 (13.6)	44.6 (13.6)	45.8 (14.0)	46.4 (12.2)
Age range (years)	18 to 82	18 to 76	19 to 76	19 to 80	19 to 80	19 to 81	20 to 76
Race							
White	217 (70%)	209 (68%)	101 (65%)	279 (91%)	284 (90%)	289 (92%)	144 (92%)
Asian	70 (23%)	83 (27%)	42 (27%)	9 (3%)	14 (4%)	10 (3%)	3 (2%)
Other	22 (7%)	16 (5%)	12 (8%)	19 (6%)	16 (5%)	14 (4%)	9 (%)
Weight (kg)	88.53 (23.87)	88.87 (24.09)	87.50 (26.04)	89.35 (22.12)	88.35 (21.23)	87.97 (21.48)	88.74 (22.73)
Percent BSA	29.7 (17.44)	30.9 (17.79)	29.6 (17.28)	34.2 (18.44)	31.8 (17.16)	31.6 (16.58)	31.3 (14.75)
PASI score	20.0 (7.85)	20.7 (8.51)	19.3 (7.07)	20.5 (7.63)	19.8 (7.52)	20.2 (7.36)	20 (7.57)
DLQI	13.9 (6.68)	13.2 (6.87)	13.2 (7.25)	14.8 (7.24)	13.2 (7.03)	14.5 (7.20)	13.7 (6.98)
Previously treated with biologicals	71 (23%)	71 (23%)	35 (23%)	39 (13%)	38 (12%)	37 (12%)	20 (13%)

Previous medical conditions							
Hyper-cholesterolaemia	19 (6%)	18 (6%)	9 (6%)	19 (6%)	19 (6%)	18 (6%)	8 (5%)
Hyperlipidaemia	18 (6%)	29 (9%)	10 (6%)	17 (6%)	13 (4%)	18 (6%)	9 (6%)
Hyper-triglyceridaemia	4 (1 %)	1 (<1%)	1 (1%)	-	1 (<1%)	1 (<1%)	1 (1%)
Hypertension	85 (28%)	97 (31%)	46 (30%)	76 (25%)	76 (24%)	85 (27%)	41 (26%)
Obesity	15 (5%)	25 (8%)	10 (6%)	23 (7%)	20 (6%)	22 (7%)	16 (10%)
Type 2 diabetes	21 (7%)	26 (8%)	15 (10%)	9 (3%)	9 (3%)	13 (4%)	8 (5%)

Data are n (%) or mean (standard deviation [SD]), in the ASR populations unless otherwise stated. Abbreviations: ASR: All subjects randomised; BSA: Body surface area; DLQI: Dermatology Life Quality Index; kg: kilograms; PASI: Psoriasis Area and Severity Index. Source: Reich et al 2017.[36]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Definition of study populations reSURFACE 1 and reSURFACE 2

Figure 7 illustrates the analysis populations and analysis strategy for the reSURFACE studies.

Figure 7: Analysis populations and strategy for the reSURFACE studies

Analysis populations

	Description
FAS Full Analysis Set	All randomised subjects who received at least 1 dose of study medication based on the treatment assigned
ITT Intention to Treat	All randomised subjects based on the treatment assignment
PP Per Protocol	FAS subjects who met key eligibility and evaluability criteria
LOCF Last Observation Carried Forward	FAS population where missing data were imputed using LOCF
ASaT All Subjects as Treated	All randomised subjects who received at least 1 dose of study medication based on the treatment received

Statistical approaches

		Statistical approach	Main analyses	Sensitivity analyses
Part 1 (up to Week 12)	reSURFACE 1 reSURFACE 2	Interventional statistics	**FAS** Missing as non-responders	FAS LOCF FAS MI ITT Missing as non responders PP Missing as non responders
Part 2 (Weeks 12 to 28)	reSURFACE 1	Descriptive statistics	**FAS** No missing imputation	
	reSURFACE 2	Interventional statistics / Descriptive statistics	**FAS** Missing as non-responders **FAS** No missing imputation	FAS LOCF FAS MI ITT Missing as non responders PP Missing as non responders
Part 3 (> Week 28)	reSURFACE 1 reSURFACE 2	Descriptive statistics	**FAS** No missing imputation	

Abbreviations: ASaT: All subjects as treated; FAS: full analysis set; ITT: intention to treat; LOCF: last observation carried forward; MI: Multiple imputations; PP: per protocol. Source: Reich et al 2017.[36]

Full-analysis-set (FAS), intention-to-treat (ITT) and per-protocol (PP) patient populations were specified in the study protocols for both studies. The FAS included all randomised patients who received at least one dose of study medication. The ITT population included all randomised patients on the basis of the treatment assigned. The PP population included patients in the FAS who met key eligibility and assessment criteria.

The data presented in the pivotal publication by Reich et al reflect the FAS: the other populations were used as supportive analyses and are presented in the supplementary appendix to the publication.[36] All populations were also defined in the clinical study reports (CSRs).[37,38]

The FAS was defined as follows in each part of the reSURFACE 1 and reSURFACE 2 studies:

Part 1: All randomised patients at baseline who received at least one dose of study medication.

Part 2: Patients who completed Part 1, entered Part 2, and received at least one dose of study 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).

Part 3: All patients who completed Part 2, entered Part 3, and received at least one dose of study medication.

Statistical analyses

As outlined in Figure 7, the primary and key secondary endpoints were analysed in the FAS. For these analyses, patients with missing data were treated conservatively as non-responders (non-responder imputation [NRI]).

For other secondary analyses, FAS observed data were used (no imputation of missing data) for pre-specified analyses. Additional post-hoc analyses were conducted with NRI for secondary endpoints in Parts 2 and 3.

Table 9 outlines the statistical analysis for the co-primary efficacy endpoint, key secondary endpoints and DLQI.

In both studies, a step-down multiplicity strategy was used to control the overall Type 1 error rate. For the primary hypothesis, PASI 75 and PGA at Week 12 were tested for tildrakizumab 200mg versus placebo, followed by tildrakizumab 100mg versus placebo.[36]

Planned sample sizes

Both trials were primarily sized to provide a substantial safety / tolerability database to support registration requirements. The sample size also provided enough power (>98%) for efficacy evaluation considering placebo / etanercept response rates for different outcomes of interest (PASI 75, PASI 90, PASI 100 and PGA).

Assumed effect sizes were based on the Phase IIb study of tildrakizumab.[35] Details of the planned sample sizes, which were driven by assessment of safety, are included in Table 9.

Identification and selection of study participants

Appendix D includes details of the number of participants who were eligible to enter the reSURFACE 1 and reSURFACE 2 studies and the number of participants randomised and allocated to each treatment. Information is provided around the rationale for participants who were re-randomised during the studies and those who were lost to follow-up or withdrew from the studies prematurely.

Discontinuation criteria were defined in the protocol.[36] A subject could discontinue from the studies at any time for any reason. A subject who discontinued from the trial was not replaced.

Table 9: Summary of statistical analyses in the reSURFACE 1 and reSURFACE 2 studies

Statistical analyses	reSURFACE 1 study (P010)	reSURFACE 2 study (P011)
Hypothesis for primary efficacy objective	Tildrakizumab is superior to placebo in the treatment of moderate to severe chronic plaque psoriasis as measured by the proportion of subjects achieving a PASI 75 response and a PGA score of 'clear' or 'minimal', with at least a two-grade reduction from baseline at Week 12.	
Statistical analysis for primary efficacy endpoints	The primary endpoints of PASI 75 response rate at Week 12 and the proportion of subjects with PGA score of 'clear' or 'minimal' with at least a two-grade reduction from baseline at Week 12 were analysed using the Cochrane-Mantel-Haenszel (CMH) test, stratified by body weight (≤90kg, >90kg) and prior exposure to biological therapy for psoriasis. Subjects with missing data were treated as non-responders. Each dose of tildrakizumab was compared to placebo at Week 12. The study was declared positive if the 200mg dose of tildrakizumab was superior to placebo on both primary endpoints when considering the FAS. The reported percent differences in effect sizes represent absolute differences. An ITT and a PP analysis were also performed as supportive analyses using the same CMH test with subjects with missing data being treated as non-responders. A second supportive sensitivity analysis was conducted based on the FAS population, where missing data were imputed using the LOCF approach.	
Statistical analysis for key secondary efficacy endpoints and DLQI	Key secondary endpoints (outlined in Table 7) were analysed in the same way as the primary endpoints, with comparisons to placebo and etanercept. DLQI was also analysed with the CMH test, on the basis of recorded data. In reSURFACE 2, for the other secondary efficacy endpoints during Part 2, analyses were done in a similar manner as in Part 1, in which tildrakizumab 200mg and tildrakizumab 100mg were each compared with etanercept. Descriptive summary statistics by treatment were generated for participants who were re-randomised from placebo to tildrakizumab 100mg or tildrakizumab 200mg.	
Sample size, power calculation for primary endpoint	Approximately 750 subjects in total were planned to receive 2:2:1 randomised treatment assignment to: Arm A: tildrakizumab 200mg (N=300); Arm B: tildrakizumab 100mg (N=300); Arm C: placebo (N=150). Assuming a placebo rate of 10% for both PASI 75 response rate and proportion of subjects with PGA 'clear' or 'minimal' with at least a two-grade reduction from baseline, the trial has more than 99% power to detect a 57% difference between tildrakizumab and placebo in PASI 75 response rate	Approximately 1,050 subjects in total were planned to receive 2:2:1:2 randomised treatment assignment to: Arm A: tildrakizumab 200mg (N=300); Arm B: tildrakizumab 100mg (N=300), Arm C: placebo (N=150); Arm D: etanercept 50mg (N=300). With this sample size, assuming a placebo rate of 10% for both PASI 75 response and PGA 'clear' or 'minimal' with at least a two-grade reduction from baseline, the trial has more than 99% power to detect a 57% difference between tildrakizumab and placebo in PASI 75 response and to detect a 55% difference in PGA 'clear' or 'minimal' with at least a

	and to detect a 55% difference in proportion of subjects with PGA 'clear' or 'minimal' with at least a two-grade reduction from baseline, using a two-sided test at significance level of α=0.05.	two-grade reduction from baseline. In addition, a difference of 17% between a tildrakizumab dose and etanercept for PASI 75 response rate could be detected with more than 98% power assuming an etanercept rate of approximately 56%; and a difference of 20% between a tildrakizumab dose and etanercept for PGA 'clear' or 'minimal' with at least a two-grade reduction from baseline can be detected with more than 99% power assuming an etanercept rate of approximately 49%, using a two-sided test at significance level of α=0.05.
	In both reSURFACE 1 and reSURFACE 2, assuming a placebo rate of 2% for PASI 90 response, the trials had more than 99% power to detect a 30% difference between tildrakizumab and placebo in PASI 90 response rate. Furthermore, assuming a placebo rate of 1% for PASI 100 response, the trials had 99% power to detect a 10% difference between tildrakizumab and placebo in PASI 100 response rate.	
	Assuming a screen failure rate of 15%, approximately 885 subjects were to be screened in reSURFACE 1.	Assuming a screen failure rate of 15%, approximately 1,235 subjects were to be screened in reSURFACE 2.
Data management, patient withdrawals	At Week 28, subjects with <PASI 50 response (NRs) were discontinued from the study. This was pre-specified for NRs in Arms A and B but protocol amendment 1 (010-01) also allowed NRs from Arm C to be discontinued at Week 28 in order to maintain masking.	At Week 28, NRs within Arms A and B were discontinued from the study. Rs in Arm D were discontinued at Week 28.
	Subjects with missing data were treated as NRs. Patient withdrawal from the study was noted for each part. Those patients withdrawing due to adverse events, protocol violations, lost to follow up, pregnancy or patient withdrew consent, among other reasons, were considered to have discontinued the study prematurely. The power of the study reflected the anticipated premature withdrawals.	

Abbreviations: CHM: Cochrane-Mantel-Haenszel; FAS: full analysis set; ITT: intention to treat; LOCF: last observation carried forward; NR: non-responder; PASI: Psoriasis Area Severity Index; PGA: physician global assessment; PP: per protocol; R: responder. Source: Reich et al 2017.[36]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The NICE quality assessment questions were used to inform the quality assessment of reSURFACE 1 and reSURFACE 2.[39] Full details of the quality assessment are included in Appendix D, and a summary is included in Table 10.

Table 10: Quality assessment results for the reSURFACE 1 and reSURFACE 2 studies

Quality assessment criterion	reSURFACE 1	reSURFACE 2
Was the randomisation method adequate?	Low risk	Low risk
Was the allocation adequately concealed?	Low risk	Low risk
Were the groups similar at the outset of the study in terms of prognostic factors?	Low risk	Low risk
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	Low risk
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Low risk	Low risk
Is there any evidence to suggested that that the authors measured more outcomes than they reported?	Low risk	Low risk
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	Low risk
Also consider whether the authors of the study publication declared any conflicts of interest	High risk	High risk

Low risk: low risk of bias for this criterion; High risk – high risk of bias for this criterion

Potential causes of bias

The authors of the reSURFACE studies noted several study limitations. Specifically, the study design meant that non-responders in the tildrakizumab groups discontinued treatment before Part 3, this might have an impact on the low dropout rate reported in these treatment arms because subjects had already shown a response to tildrakizumab within 28 weeks of treatment. Also, given the improvements in PASI 75 and PGA responses in patients who continued treatment until Week 28, the 12 week time point might have been too early to adequately assess the efficacy potential of tildrakizumab (see section B.2.13 for further details).[36]

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Summary

- The results of the reSURFACE studies demonstrated that tildrakizumab 100mg and 200mg is an effective and well tolerated treatment for moderate to severe psoriasis, with response maintained for up to three years and the benefit of maintenance dosing only every 12 weeks.
    - As described in the SmPC, while 100mg is the recommended dose, in patients with certain characteristics (e.g. high disease burden, weight ≥90kg) a dose of 200mg may provide greater efficacy.
- The co-primary endpoints were achieved in both pivotal Phase III clinical studies, reSURFACE 1 and reSURFACE 2, with significantly higher proportions of patients treated with tildrakizumab 100mg and 200mg achieving PASI 75 and PGA responses at 12 weeks (after only two doses of tildrakizumab) compared with placebo ($p<0.001$). In the reSURFACE 2 study, significantly more patients in the tildrakizumab 100mg and 200mg groups achieved a PASI 75 response when compared with etanercept ($p\leq0.001$).
- **At week 12** (i.e. after only two doses of tildrakizumab):
    - With tildrakizumab 100mg:
        - 63.8% patients in reSURFACE 1 and 61.2% in reSURFACE 2 achieved a PASI 75 response.
        - 57.9% patients in reSURFACE 1 and 54.7% in reSURFACE 2 achieved a PGA response of ‘clear’ or ‘minimal’.
    - With tildrakizumab 200mg:
        - 62.3% patients in reSURFACE 1 and 65.6% in reSURFACE 2 achieved a PASI 75 response.
        - 59.1% patients in reSURFACE 1 and 59.2% in reSURFACE 2 achieved a PGA response of ‘clear’ or ‘minimal’.
    - A higher proportion of patients who received tildrakizumab 100mg and 200mg achieved a PASI 90 and PASI 100 response compared with patients who received placebo ($p<0.001$; reSURFACE 1 and 2) or etanercept ($p\leq0.001$; reSURFACE 2).

- In both studies, the proportions of patients with PASI 75 and PGA responses of 'clear' or 'minimal' continued to increase from Week 12 through to Week 28 following only one additional dose of tildrakizumab.
- **At Week 28** (after three doses of tildrakizumab):
    - With tildrakizumab 100mg:
        - 76.6% and 73.5% of patients achieved a PASI 75 response in reSURFACE 1 and 2 respectively;
        - 62.9% and 64.6% of patients achieved a PGA response of 'clear' or 'minimal' in reSURFACE 1 and 2, respectively
    - With tildrakizumab 200mg:
        - 79.2% and 72.6% of patients achieved a PASI 75 response in reSURFACE 1 and 2 respectively
        - 66.8% and 69.2% of patients achieved a PGA response of 'clear' or 'minimal' in reSURFACE 1 and 2, respectively
    - In reSURFACE 2, for endpoints (PASI 75, 90 and 100 and PGA 'clear' or 'minimal'), response rates at Week 28 were significantly higher in the tildrakizumab 100mg and 200mg groups compared with the etanercept group ($p<0.001$).
- **Maintenance of response:** Tildrakizumab maintained clinical efficacy over time in patients who achieved a PASI 75 response at Week 28:
    - At Week 64, PASI 75 response was maintained in 87.5% and 93.9% of subjects receiving tildrakizumab 100mg and 200mg, respectively, in reSURFACE 1. The corresponding figures at Week 52 in reSURFACE 2 were 93.6% and 97.1%, respectively.
- Pooled data from the reSURFACE 1 and 2 long term extension studies showed that efficacy was maintained for up to three years
    - After Week 148, 91% and 92% of patients on maintenance treatment with tildrakizumab 100mg and 200mg, respectively, were PASI 75 responders and 68% and 69% were PASI 90 responders.
- **Quality of life:** Tildrakizumab was associated with statistically significant improvement in health-related QoL as assessed by the DLQI and improvements were maintained over time.

B.2.6.2 Pivotal Phase III clinical data – reSURFACE 1 and 2

The Reich et al publication of the reSURFACE studies focuses on efficacy and safety during the first 28 weeks of treatment (Parts 1 and 2). Only top-line results are reported in the publication for patients during Part 3 of the study.[36] Additional data have been provided from the relevant CSRs[37,38] and data on file.[40,41]

The clinical efficacy data in the publication are based on the FAS.[36] Data from the ITT analysis of the primary and secondary endpoints at 12 weeks from reSURFACE 1 and reSURFACE 2 are included in the online supplementary appendix to the publication.[36] These ITT data were identical to the data from the FAS during Part 1 of the study as the populations for both analyses were identical.

Therefore, only the FAS results are presented within this submission. Data from the ITT analysis of the secondary efficacy endpoints at Week 28 are also included in the publication appendix for reSURFACE 2.[36] The data are similar to that of the FAS with some exceptions, for example the ITT population for the tildrakizumab 200mg group, which includes 300 patients whereas the FAS includes data from 299 patients during Part 2 of the study. The results presented below (Section B.2.6.3) clearly state where observed data have been presented and where missing data have been imputed as non-responder data.

The Part 1 results will be presented for both reSURFACE studies, followed by results for Part 2 and Part 3.

B.2.6.3 Clinical effectiveness - Part 1 of the reSURFACE studies: Co-primary and secondary endpoints at Week 12

reSURFACE 1 Part 1 (Week 12)

The reSURFACE 1 study achieved both of its co-primary endpoints:

- A significantly higher proportion of patients in both the tildrakizumab 100mg and 200mg groups compared with the placebo group achieved a PASI 75 response and a PGA score of ‘clear’ or ‘minimal’, with at least a two-grade reduction from baseline at Week 12 ($p<0{\cdot}001$; Table 11).[36,37]

Table 11: Primary efficacy endpoints at Week 12 in Part 1 of reSURFACE 1 (FAS)

Primary Endpoint (NRI)	Tildrakizumab 100mg (N=309)	Tildrakizumab 200mg (N=308)	Placebo (N=154)
PASI 75			
Responders, n (%)	197 (63.8%)	192 (62.3%)	9 (5.8%)
% difference from placebo	58.0%	56.6%	N/A
95% CI; p value	51.0 to 64.1; p<0.001	49.6 to 62.8; p<0.001	
Clear or minimal PGA			
Responders, n (%)	179 (57.9%)	182 (59.1%)	11 (7.1%)
% difference from placebo	50.9%	52.1%	N/A
95% CI; p value	43.6 to 57.4; p<0.001	44.8 to 58.5; p<0.001	

The FAS population included all randomly assigned patients who received at least one dose of study medication. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90kg versus >90kg) and previous exposure to biological therapy for psoriasis with sample size weights. p values were calculated with the CMH test and stratified by bodyweight and exposure to biological therapies; p values were not adjusted for multiplicity. NRI was pre-specified for missing data and is shown for all data. Abbreviations: CI: confidence interval; CMH: Cochrane-Mantel-Haenszel; N/A: not applicable; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment. Source: Reich et al 2017 and reSURFACE 1 CSR.[36,37]

Key secondary endpoints are provided in Table 12. At Week 12, the proportions of patients achieving PASI 90 and PASI 100 responses were significantly higher in the tildrakizumab 100mg and 200mg groups than in the placebo group (p<0·001).[36,37]

Table 12: Key secondary efficacy endpoints at Week 12 in Part 1 of reSURFACE 1 (FAS)

Secondary Endpoint (NRI)	Tildrakizumab 100mg (N=309)	Tildrakizumab 200mg (N=308)	Placebo (N=154)
PASI 90			
Responders, n (%)	107 (34.6%)	109 (35.4%)	4 (2.6%)
% difference from placebo	32.1%	32.9%	N/A
95% CI; p value	25.9 to 38.0; p<0.001	26.8 to 38.8; p<0.001	
PASI 100			
Responders, n (%)	43 (13.9%)	43 (14.0%)	2 (1.3%)
% difference from placebo	12.7%	12.7%	N/A
95% CI; p value	8.0 to 17.3; p<0.001	8.3 to 17.2; p<0.001	

The FAS population included all randomly assigned patients who received at least one dose of study medication. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90kg versus >90kg) and previous exposure to biological therapy for psoriasis with sample size weights. p values were calculated with the CMH test and stratified by bodyweight and exposure to biological therapies; p values were not adjusted for multiplicity. NRI was pre-specified for missing data and is shown for all data. Abbreviations: CI: confidence Interval; CMH: Cochrane-Mantel-Haenszel; N/A: not applicable; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index. Source: Reich et al 2017 and reSURFACE 1 CSR.[36,37]

reSURFACE 2 Part 1 (Week 12)

The reSURFACE 2 study achieved both of its co-primary endpoints (Table 13).[36,38]

- A significantly higher proportion of patients in the tildrakizumab 100mg and 200mg groups than in the placebo group achieved a PASI 75 response and a PGA score of 'clear' or 'minimal', with at least a two-grade reduction from baseline at Week 12 (p<0·001).
- A significantly higher proportion of patients in the tildrakizumab 100mg and 200mg groups achieved a PASI 75 response (p≤0.001) at Week 12 compared with the etanercept group.
- A significantly higher proportion of patients in the tildrakizumab 200mg group achieved a PGA response (p<0.05) at Week 12 compared with the etanercept group.

Table 13: Primary efficacy endpoints at Week 12 in Part 1 of reSURFACE 2 (FAS)

Primary Endpoint (NRI)	Tildrakizumab 100mg (N=307)	Tildrakizumab 200mg (N=314)	Placebo (N=156)	Etanercept (N=313)
PASI 75				
Responders, n (%)	188 (61.2%)	206 (65.6%)	9 (5.8%)	151 (48.2%)
% difference from placebo (95% CI; p value)	55.5% (48.3 to 61.8; p<0.001)	59.8% (52.9 to 65.9; p<0.001)	N/A	N/A
% difference from etanercept (95% CI; p value)	13.1% (5.3 to 20.7; p=0.001)	17.4% (9.7 to 24.9; p<0.001)	N/A	N/A
Clear or minimal PGA				
Responders, n (%)	168 (54.7%)	186 (59.2%)	7 (4.5%)	149 (47.6%)
% difference from placebo (95% CI; p value)	50.2% (43.2 to 56.5; p<0.001)	54.7% (47.9 to 60.8; p<0.001)	N/A	N/A
% difference from etanercept (95% CI; p value)	7.3% (-0.5 to 15.0; p=0.0663)	11.7% (4.0 to 19.3; p<0.05)	N/A	N/A

The FAS population included all randomly assigned patients who received at least one dose of study medication. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90kg versus >90kg) and previous exposure to biological therapy for psoriasis with sample size weights. p values were calculated with the CMH test and stratified by bodyweight and exposure to biological therapies; p values were not adjusted for multiplicity. NRI was pre-specified for missing data and is shown for all data. Abbreviations: CI: confidence interval; CMH: Cochrane-Mantel-Haenszel; PASI: Psoriasis Area and Severity Index; N/A: not applicable; NRI: non-responder imputation; PGA: Physician's Global Assessment. Source: Reich et al 2017 and reSURFACE 2 CSR.[36,38]

Key secondary efficacy endpoints are provided in Table 14. At Week 12, the proportions of patients achieving PASI 90 and PASI 100 responses were significantly higher in the tildrakizumab 200mg group than in the placebo (p<0.001) and etanercept groups (p≤0·001).[36,38]

Table 14: Key secondary efficacy endpoints at Week 12 in Part 1 of reSURFACE 2 (FAS)

Secondary Endpoint (NRI)	Tildrakizumab 100mg (N=307)	Tildrakizumab 200mg (N=314)	Placebo (N=156)	Etanercept (N=313)
PASI 90				
Responders, n (%)	119 (38.8%)	115 (36.6%)	2 (1.3%)	67 (21.4%)
% difference from placebo (95% CI; p value)	37.5% (31.1 to 43.4; p<0.001)	35.3% (29.2 to 41.1; p<0.001)	N/A	N/A
% difference from etanercept (95% CI; p value)	17.4% (10.3 to 24.4; p<0.001)	15.2% (8.3 to 22.1; p<0.001)	N/A	N/A
PASI 100				
Responders, n (%)	38 (12.4%)	37 (11.8%)	0	15 (4.8%)
% difference from placebo (95% CI; p value)	12.4% (8.5 to 16.6; p<0.001)	11.7% (7.8 to 16.0; p<0.001)	N/A	N/A
% difference from etanercept (95% CI; p value)	7.6% (3.3 to 12.3; p<0.001)	7.0% (2.8 to 11.6; p=0.001)	N/A	N/A

The FAS population included all randomly assigned patients who received at least one dose of study medication. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90kg versus >90kg) and previous exposure to biological therapy for psoriasis with sample size weights. p values were calculated with the CMH test and stratified by bodyweight and exposure to biological therapies; p values were not adjusted for multiplicity. NRI was pre-specified for missing data and is shown for all data. Abbreviations: CI: Confidence Interval; CMH: Cochran-Mantel-Haenszel; N/A: not applicable; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index. Source: Reich et al 2017 and reSURFACE 2 CSR.[36,38]

B.2.6.4 Clinical effectiveness - Part 2 of the reSURFACE studies: secondary endpoints at Week 28

reSURFACE 1 Part 2 (Week 28)

Table 15 shows a post hoc analysis of the secondary efficacy endpoints at Week 28 from the FAS population for all patients entering Part 2 of reSURFACE 1 who received at least one dose of study medication.

In both the 100mg and 200mg tildrakizumab groups, the proportions of patients with PASI 75, PASI 90 and PASI 100 responses and those with a PGA response continued to increase from Week 12 through to Week 28.

In subjects randomised to placebo in Part 1 and re-randomised to tildrakizumab in Part 2, PASI 75, 90 and 100 responses and the PGA response increased from Week 12 to Week 28. At Week 28, similar proportions of patients with a response were observed between these groups and the groups of patients who received tildrakizumab (100mg or 200mg) from the start of the trial (Table 15).[36,37]

Table 15: Secondary efficacy endpoints at Week 28 in Part 2 of reSURFACE 1 (FAS)

Secondary Endpoint	Tildrakizumab 100mg (N=299)*	Tildrakizumab 200mg (N=298)*	Placebo to tildrakizumab 100mg (N=74)*	Placebo to tildrakizumab 200mg (N=72)*
PASI 75				
Observed data	229 (80.4%)	236 (81.9%)	54 (77.1%)	56 (86.2%)
Non-responder imputation	229 (76.6%)	236 (79.2%)	54 (73.0%)	56 (77.8%)
Clear or minimal PGA				
Observed data	188 (66.0%)	199 (69.1%)	53 (75.7%)	46 (70.8%)
Non-responder imputation	188 (62.9%)	199 (66.8%)	53 (71.6%)	46 (63.9%)
PASI 90				
Observed data	147 (51.6%)	170 (59.0%)	41 (58.6%)	34 (52.3%)
Non-responder imputation	147 (49.2%)	170 (57.0%)	41 (55.4%)	34 (47.2%)
PASI 100				
Observed data	67 (23.5%)	91 (31.6%)	22 (31.4%)	17 (26.2%)
Non-responder imputation	67 (22.4%)	91 (30.6%)	22 (29.7%)	17 (23.6%)

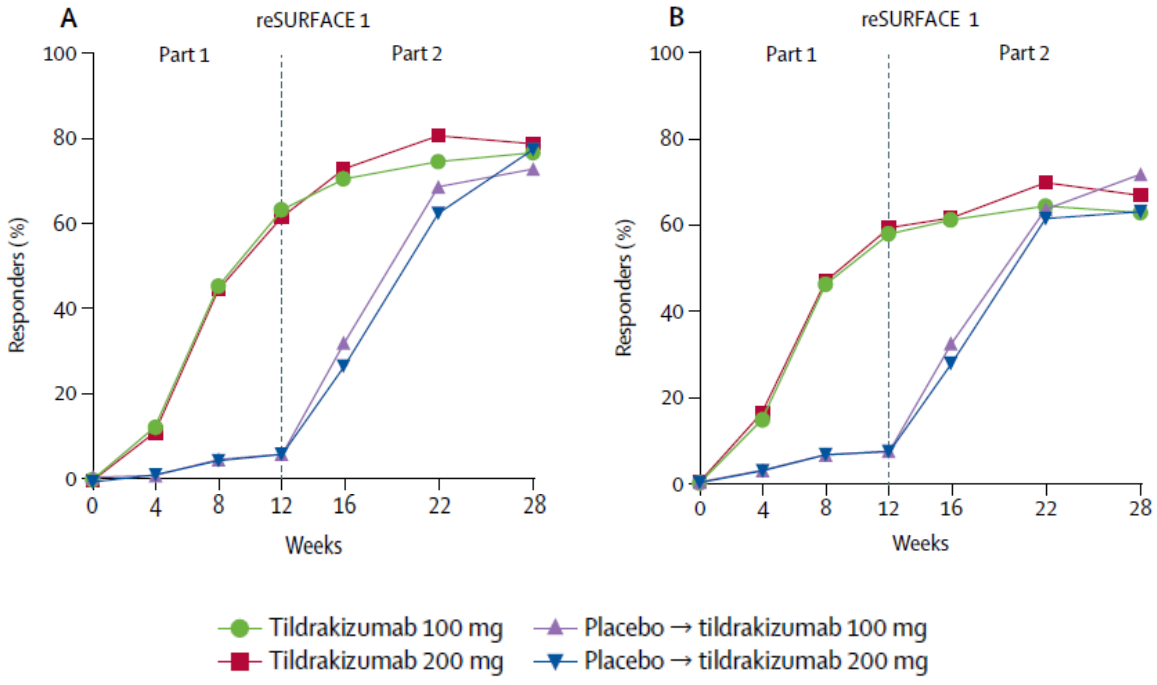
Data are n (%). The FAS population included all patients entering Part 2 who received at least one dose of study medication. NRI was pre-specified and is shown for key secondary outcomes. Post-hoc analyses for PASI 75, PGA, PASI 90 and PASI 100 at Week 28 were done with NRI. Observed data were pre-specified for all other secondary outcomes. Observed data was derived from randomised subjects who received at least one dose of study medication in Part 2 of the study and with a valid value at baseline and at the time point for the endpoint. These numbers were tildrakizumab 100mg [redacted], tildrakizumab 200mg [redacted], placebo to tildrakizumab 100mg [redacted] and placebo to tildrakizumab 200mg [redacted] for all analyses. *Numbers shown include participants with missing data. Abbreviations: NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment. Source: Reich et al 2017 and reSURFACE 1 CSR.[36,37]

The proportion of patients achieving PASI 75 and PGA 'clear' or 'minimal' with at least a two-grade reduction in reSURFACE 1 and 2 up to week 28 is shown in Figure 8.

Patients who did not respond to tildrakizumab by Week 28 were discontinued from reSURFACE 1 at that time point. The percentage of patients on tildrakizumab 100mg

and 200mg who discontinued due to lack of efficacy at Week 28 was 3.9% (12/309) and 1.3% (4/308), respectively.[36,37]

Figure 8: Proportion of patients achieving a PASI 75 and PGA 'clear' or 'minimal with at least a two-grade reduction in Parts 1 and 2 of reSURFACE 1



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.[36]

reSURFACE 2 Part 2 (Week 28)

Table 16 shows the secondary efficacy endpoints at Week 28 from the FAS population for all patients entering Part 2 of reSURFACE 2 who received at least one dose of study medication.

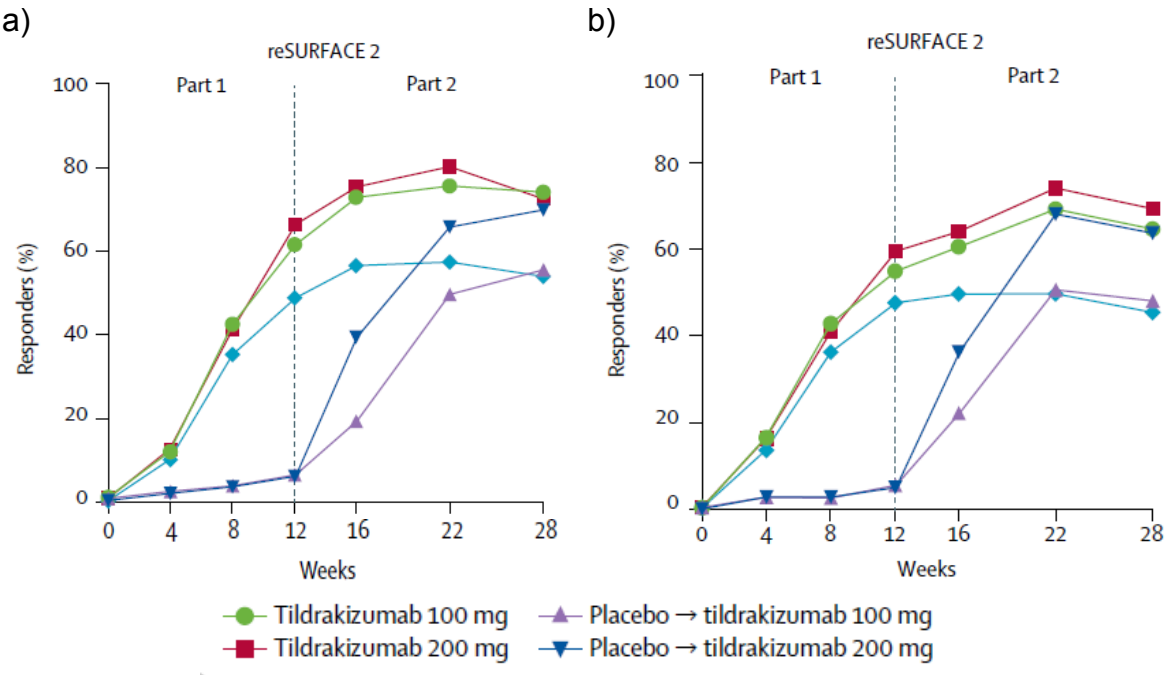
In the tildrakizumab groups, the proportions of patients with PASI 75, 90 and 100 responses and those with a PGA response continued to increase from Week 12 through to Week 28. For these endpoints, the response rates at Week 28 were significantly higher in both the tildrakizumab 100mg and 200mg groups compared with the etanercept group ($p<0.001$).[36,38]

In patients randomised to placebo in Part 1 and re-randomised to tildrakizumab in Part 2, PASI 75, 90 and 100 responses and PGA response increased from Week 12 to Week 28.[36,38]

Among patients receiving tildrakizumab from baseline to Week 28, PASI 75 and PGA responses peaked at Week 22 (Figure 9).[36,38]

As in reSURFACE 1, patients who did not respond to tildrakizumab by Week 28 were discontinued from reSURFACE 2 at that time point. The percentage of patients on tildrakizumab 100mg and 200mg who discontinued due to lack of efficacy at Week 28 was 0.7% (2/307) and 0.3% (1/314).[36,38]

Figure 9: Proportion of patients achieving a PASI 75 response and PGA 'clear' or 'minimal' with at least two-grade reduction in Parts 1 and 2 of reSURFACE 2



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.[36]

Table 16: Secondary efficacy endpoints at Week 28 in Part 2 of reSURFACE 2 (FAS)

Secondary Endpoint	Tildrakizumab 100mg (N=294)*	Tildrakizumab 200mg (N=299)*	Placebo to tildrakizumab 100mg (N=69)*	Placebo to tildrakizumab 200mg (N=72)*	Etanercept (n=289)*
PASI 75 (NRI)					
n (%)	216 (73.5%)	217 (72.6%)	38 (55.1%)	50 (69.4%)	155 (53.6%)
% difference from etanercept (95% CI; p value)	20.1% (12.4 to 27.6; p<0.001)	19.2% (11.5 to 26.7; p<0.001)	N/A	N/A	N/A
Clear or minimal PGA (NRI)					
n (%)	190 (64.6%)	207 (69.2%)	33 (47.8%)	46 (63.9%)	131 (45.3%)
% difference from etanercept (95% CI; p value)	19.6% (11.7 to 27.3; p<0.001)	24.1% (16.2 to 31.7; p<0.001)	N/A	N/A	N/A
PASI 90 (OD)					
Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	161 (55.5%)	169 (57.7%)	26 (39.4%)	33 (48.5%)	85 (30.7%)
% difference from etanercept (95% CI; p value)	24.9% (17.0 to 32.6; p<0.001)	27.1% (19.1 to 34.7; p<0.001)	N/A	N/A	N/A
PASI 90 (NRI)					
n (%)	161 (54.8%)	169 (56.5%)	26 (37.7%)	33 (45.8%)	85 (29.4%)
% difference from etanercept (95% CI; p value)	25.5% (17.6 to 33.0; p<0.001)	27.3% (19.5 to 34.7; p<0.001)	N/A	N/A	N/A
PASI 100 (OD)					
Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
n (%)	66 (22.8%)	79 (27.0%)	9 (13.6%)	13 (19.1%)	31 (11.2%)
% difference from etanercept (95% CI; p value)	11.7% (5.6 to 17.9; p<0.001)	15.7% (9.4 to 22.1; p<0.001)	N/A	N/A	N/A
PASI 100 (NRI)					
n (%)	66 (22.4%)	79 (26.4%)	9 (13.0%)	13 (18.1%)	31 (10.7%)
% difference from etanercept (95% CI; p value)	11.8% (5.9 to 17.9; p<0.001)	15.7% (9.6 to 22.0; p<0.001)	N/A	N/A	N/A

The FAS population included all patients entering Part 2 who received at least one dose of study medication. NRI was pre-specified and is shown for key secondary outcomes. Observed data were pre-specified for all other secondary outcomes. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90kg versus >90kg) and previous exposure to biological therapy for psoriasis with sample size weights. p values were calculated with the CMH and stratified by bodyweight and exposure to biological therapies; p values were not adjusted for multiplicity. Post-hoc analyses for PASI 90 and PASI 100 at Week 28 were done with NRI. *Numbers shown include participants with missing data. Abbreviations: CMH: Cochran-Mantel-Haenszel; N/A: not applicable; NRI: non-responder imputation; OD: observed data; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment. Source: Reich et al 2017 and reSURFACE 2 CSR.[36,38]

Appropriate Timepoint to assess treatment response

NICE usually advises that patients should be assessed for continued treatment at defined time points. In the case of tildrakizumab Almirall suggest this should be at 28 weeks, for the following reasons:

- Tildrakizumab doses are administered at 0, 4 and 16 weeks.
- Based on the key secondary end points (Week 28 data), patients continued to have a clinically relevant improvement beyond week 12 (pivotal studies primary end point).
- To implement an assessment at 12 weeks would require clinicians to bring patients back to the outpatients clinic at a time point when they would not otherwise have been assessed, hence additional costs.
- Based on the trial data, a large proportion of patients being assessed at week 12 using the usual assessment criteria (PASI 75 or PASI 50 plus ≥5 point reduction in DLQI) would meet the test for continuation.
- The SmPC states: “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”.[1]

Our conclusion is that it would be biologically implausible, evidently premature, and clinically burdensome to specialists and patients, to implement an assessment and stopping rule at week 12. Therefore, Almirall proposes an assessment time point at 28 weeks. This would be based on evidence derived from the multiplicity-adjusted efficacy outcomes of key secondary endpoints.

B.2.6.5 Clinical effectiveness in Part 3 of the reSURFACE studies: Maintenance and durability of effect

reSURFACE 1: Part 3 (Week 64) in Week 28 responders

In patients in the tildrakizumab groups who continued on the same dose throughout Part 3 of reSURFACE 1, the proportion of patients with a PASI 75 response remained high between Weeks 28 and 64.[37] In a pre-specified analysis of observed data, [redacted] of Week 28 responders in the tildrakizumab 100mg group and [redacted] of Week 28 responders in the tildrakizumab 200mg group still had a PASI 75 response at Week 64. The corresponding figures for PGA response were 69 of 112 (61.6%) and 87 of 114 (76.3%) in the tildrakizumab 100mg and 200mg groups at Week 64, respectively (Figure 10, Figure 11 and see Appendix M for further details).[36,37]

Figure 10: Efficacy over time in tildrakizumab 100mg Week 28 PASI 75 responders in reSURFACE 1

Tildrakizumab 100mg		Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64
PASI 75	Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA response	Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Graph shows the proportion of subjects with a PASI 75 response and a PGA response in Part 3 of reSURFACE 1 for subjects randomised to tildrakizumab 200mg in Part 1 who were PASI 75 responders at Week 28. Proportion of subjects is calculated from the number of responders at that visit relative to the number of randomised subjects who received at least one dose of study medication in study part and with valid value at baseline and at the time point for endpoint (see Appendix M for further details). Observed data with no imputation of missing data. Abbreviations: PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment. Source: reSURFACE 1 CSR.[37]

Figure 11: Efficacy over time in tildrakizumab 200mg Week 28 PASI 75 responders in reSURFACE 1

Tildrakizumab 200mg		Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 56	Week 60	Week 64
PASI 75	Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA response	Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Graph shows the proportion of subjects with a PASI 75 response and a PGA response in Part 3 of reSURFACE 1 for subjects randomised to tildrakizumab 200mg in Part 1 who were PASI 75 responders at Week 28. Proportion of subjects is calculated from the number of responders at that visit relative to the number of randomised subjects who received at least one dose of study medication in study part and with valid value at baseline and at the time point for endpoint (see Appendix M for further details). Observed data with no imputation of missing data. Abbreviations: PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment. Source: reSURFACE 1 CSR.[37]

Observed data illustrates that for patients receiving tildrakizumab 100mg and 200mg who achieved a PASI 75 response at Week 28, a PASI 90 response was observed in [redacted](58.0%) and [redacted](74.6%) of patients at Week 64. The corresponding figures for PASI 100 response were [redacted](32.1%) and [redacted](40.4%) in the 100mg and 200mg tildrakizumab groups, respectively[1,37]

reSURFACE 2: Part 3 (Week 52) in Week 28 responders

Patients continuing on tildrakizumab throughout the study

In patients in the tildrakizumab groups who continued on that dose throughout Part 3 of the study, the proportions of patients with a PASI 75 response remained high between Weeks 28 and 52. In a pre-specified analysis of observed data, [redacted] of Week 28 responders in the tildrakizumab 100mg group and [redacted] of Week 28 responders in the tildrakizumab 200mg group still had a PASI 75 response at Week 52. The corresponding figures for PGA response were 162 of 204 (79.4%) and 89 of 105 (84.8%) in the tildrakizumab 100mg and 200mg groups at Week 52, respectively (Figure 12, Figure 13 and see Appendix M for further details).[36,38]

Figure 12: Efficacy over time in tildrakizumab 100mg Week 28 PASI 75 responders in reSURFACE 2

Tildrakizumab 100mg		Week 32	Week 36	Week 40	Week 46	Week 52
PASI 75	Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA response	Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Graph shows the proportion of subjects with a PASI 75 response and a PGA response in Part 3 of reSURFACE 2 for subjects randomised to tildrakizumab 200mg in Part 1 who were PASI 75 responders at Week 28. Proportion of subjects is calculated from the number of responders at that visit relative to the number of randomised subjects who received at least one dose of study medication in study part and with valid value at baseline and at the time point for endpoint (see Appendix M for further details). Observed data with no imputation of missing data. Abbreviations: PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment. Source: reSURFACE 2 CSR.[38]

Figure 13: Efficacy over time in tildrakizumab 200mg Week 28 PASI 75 responders in reSURFACE 2

Tildrakizumab 200mg		Week 32	Week 36	Week 40	Week 46	Week 52
PASI 75	Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PGA response	Subjects with data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Graph shows the proportion of subjects with a PASI 75 response and a PGA response in Part 3 of reSURFACE 2 for subjects randomised to tildrakizumab 200mg in Part 1 who were PASI 75 responders at Week 28. Proportion of subjects is calculated from the number of responders at that visit relative to the number of randomised subjects who received at least one dose of study medication in study part and with valid value at baseline and at the time point for endpoint (see Appendix M for further details). Observed data with no imputation of missing data. Abbreviations: PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment. Source: reSURFACE 2 CSR.[38]

Observed data illustrate that for patients receiving tildrakizumab 100mg and 200mg who achieved a PASI 75 response at Week 28, PASI 90 response was maintained in 160 of 204 (78.4%) and 86 of 105 (81.9%) of patients at Week 52. The corresponding figures for PASI 100 maintenance were 72 of 204 (35.3%) and 49 of 105 (46.7%) in the 100mg and 200mg tildrakizumab groups, respectively.[1,38]

Patients randomised to etanercept in Part 1 who crossed over to tildrakizumab in Part 3

Etanercept non responders or partial responders who entered Part 3 of the study were crossed over to tildrakizumab 200mg and received their first dose at Week 32, additional doses were given at Weeks 36, and 48.[38] In this group:

- The proportion of subjects with a PASI 75 response at week 52 was 81.4%
- PGA response of [redacted] at Week 52.

These data support the hypothesis that patients who have failed previous treatment may subsequently respond to tildrakizumab and further supports the rationale for increased treatment options for patients with psoriasis. In clinical practice options become limited once patients fail first-line treatment, these data indicate that tildrakizumab could be considered an option in patients who have failed previous treatment.

B.2.6.6 Long term effectiveness in patients from reSURFACE 1 and reSURFACE 2

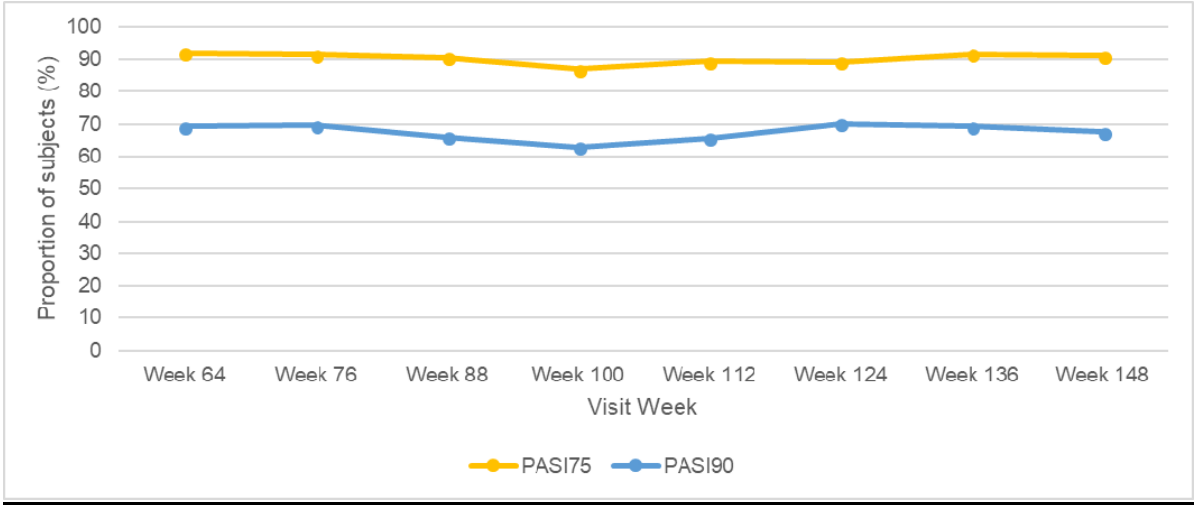
reSURFACE 1 and reSURFACE 2 had an optional long term open-label extension study (192 weeks) after the period of 64 weeks in reSURFACE 1 and 52 weeks in reSURFACE 2. In both extension studies, patients who completed the base study and achieved at least a PASI 50 response received the same dose of tildrakizumab (100mg or 200mg every 12 weeks) that they were receiving at the completion of the base study.[37,38]

Results from the long term extension studies demonstrate that the response to tildrakizumab 100mg and 200mg is maintained for up to three years.[1,40]

Pooled data from reSURFACE 1 and re-SURFACE 2 (Figure 14 and Figure 15) demonstrate that 89.4% of patients re-randomised to maintenance treatment with tildrakizumab 100mg and 91.7% of patients re-randomised to tildrakizumab 200mg were still PASI 75 responders at two years (Week 112). These responses were maintained at three years, with 91.2% of patients in the tildrakizumab 100mg group and 92.4% in the tildrakizumab 200mg group having a PASI 75 response at Week 148.[40]

The corresponding maintenance figures for PASI 90 response were 65.7% and 73.0% in the tildrakizumab 100mg and 200mg groups, respectively, at two years and 67.6% and 69.0% in the tildrakizumab 100mg and 200mg groups, respectively, at three years (Figure 14 and Figure 15).[40]

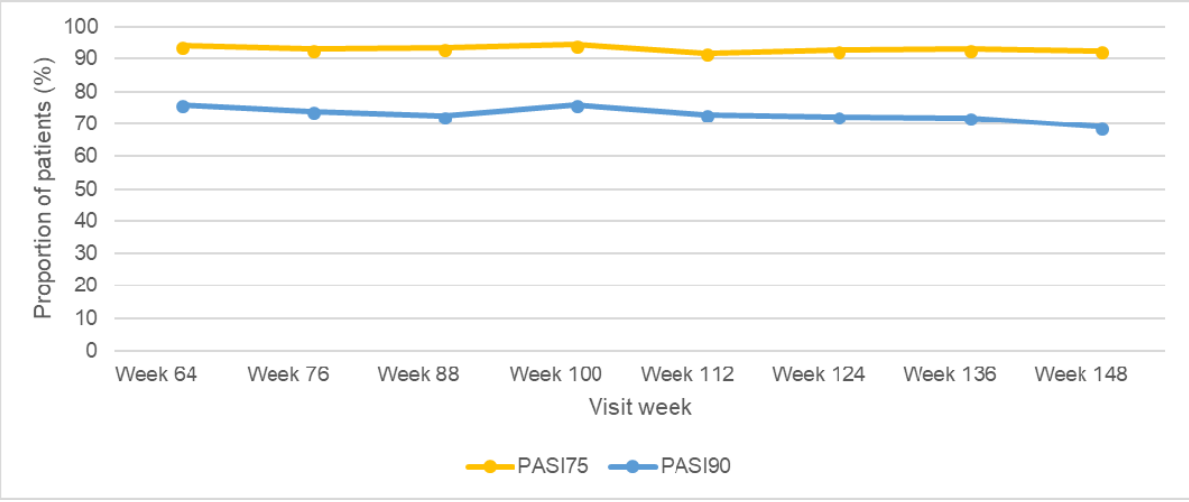
Figure 14: Long term PASI 75 and PASI 90 responses in subjects re-randomised to maintenance treatment with tildrakizumab 100mg (pooled data from reSURFACE 1 and reSURFACE 2)



Tildrakizumab 100mg		Week 64	Week 76	Week 88	Week 100	Week 112	Week 124	Week 136	Week 148
PASI 75	Subjects with data	300	297	289	287	283	278	267	262
PASI 90	Subjects with data	300	297	289	287	283	278	267	262

Data represents the FAS within the two-year extension study in patients who were PASI 75 responders at Week 28. No imputation of missing data. The numbers in the table below the graph represent the number of patients with observed data at each time point. Source: Almirall data on file 2018.[40]

Figure 15: Long term PASI 75 and PASI 90 responses in subjects re-randomised to maintenance treatment with tildrakizumab 200mg (pooled data from reSURFACE 1 and reSURFACE 2)



Tildrakizumab 200mg		Week 64	Week 76	Week 88	Week 100	Week 112	Week 124	Week 136	Week 148
PASI 75	Subjects with data	213	211	211	209	204	202	199	197
PASI 90	Subjects with data	213	211	211	209	204	202	199	197

Data represents the FAS within the two-year extension study in patients who were PASI 75 responders at Week 28. No imputation of missing data. The numbers in the table below the graph represent the number of patients with observed data at each time point. Source: Almirall data on file 2018.[40]

B.2.6.7 Impact of tildrakizumab on quality-of-life

The Part 1 and 2 results will be presented for both reSURFACE studies, followed by results for Part 3.

DLQI: Parts 1 and 2 of the reSURFACE studies

Throughout Parts 1 and 2 of reSURFACE 1 and reSURFACE 2 tildrakizumab was associated with statistically significant improvements in health-related QoL as assessed by the DLQI.

reSURFACE 1

In reSURFACE 1, the proportion of patients achieving a DLQI score of 0 or 1 was significantly higher in the tildrakizumab 100mg (41.4%) and 200mg groups (44.1%) than in the placebo group (5.3%) at Week 12 (Table 17; p<0.001).[36,37]

The proportion of patients achieving a DLQI score of 0 or 1 increased between Week 12 and Week 28 from 41.4% (126 of 304 patients with data) to 52.4% (152 of 290 patients with data) in patients who continued on tildrakizumab 100mg throughout Part 2. The corresponding figures for patients continuing on tildrakizumab 200mg throughout Part 2 were 44.1% (132 / 299 patients with data) to 56.7% (164 / 289 patients with data) (Table 18).[36,37]

Table 17: DLQI score of 0 or 1 at Week 12 in Part 1 of reSURFACE 1

DLQI score 0 or 1 (OD)	Tildrakizumab 100mg (N=309)	Tildrakizumab 200mg (N=308)	Placebo (N=154)
Subjects with data	304	299	150
Responders, n (%)	126 (41.4%)	132 (44.1%)	8 (5.3%)
% difference from placebo	36.1%	38.9%	N/A
95% CI; p value	29.3 to 42.5; p<0.001	31.9 to 45.4; p<0.001	

The FAS population included all randomly assigned patients who received at least one dose of study medication. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90kg versus >90kg) and previous exposure to biological therapy for psoriasis with sample size weights. p values were calculated with the CMH test and stratified by bodyweight and exposure to biological therapies; p values were not adjusted for multiplicity. DLQI is calculated relative to observed data. Abbreviations: CI: confidence Interval; CMH: Cochrane-Mantel-Haenszel; DLQI: Dermatology Life Quality Index; N/A: not applicable; OD: observed data. Source: Reich et al 2017 and reSURFACE 1 CSR.[36,37]

Table 18: DLQI score of 0 or 1 at Week 28 in Part 2 of reSURFACE 1

DLQI score 0 or 1 (OD)	Tildrakizumab 100mg (N=299)*	Tildrakizumab 200mg (N=298)*	Placebo to tildrakizumab 100mg (N=74)*	Placebo to tildrakizumab 200mg (N=72)*
Subjects with data	290	289	71	68
Observed data	152 (52.4%)	164 (56.7%)	37 (52.1%)	38 (55.9%)

Data are n (%). The FAS population included all patients entering Part 2 who received at least one dose of study medication. Observed data were pre-specified and were derived from randomised subjects who received at least one dose of study medication in Part 2 of the study and with valid values at baseline and at the time point for the endpoint. Abbreviations: DLQI = Dermatology Life Quality Index; OD: observed data. *Numbers shown include participants with missing data. Source: Reich et al 2017.[36]

reSURFACE 2

In reSURFACE 2, the proportion of patients achieving a DLQI score of 0 or 1 was significantly higher in the tildrakizumab 100mg (40.2%) and 200mg groups (47.4%) compared with the placebo group (8.0%; p<0.001) at Week 12. The proportion of patients achieving a DLQI score of 0 or 1 was also significantly higher in the tildrakizumab 200mg group than in the etanercept group (35.5%; p=0.003) at Week 12 (Table 19).[36,38]

Table 19: DLQI score of 0 or 1 at Week 12 in Part 1 of reSURFACE 2

DLQI score 0 or 1 (OD)	Tildrakizumab 100mg (N=307)	Tildrakizumab 200mg (N=314)	Placebo (N=156)	Etanercept (N=313)
Subjects with data	296	306	150	304
Responders, n (%)	119 (40.2%)	145 (47.4%)	12 (8.0%)	108 (35.5%)
% difference from placebo (95% CI; p value)	32.1% (24.5 to 39.1; p<0.001)	39.3% (31.8 to 46.1; p<0.001)	N/A	N/A
% difference from etanercept (95% CI; p value)	4.8% (-2.9 to 12.5; p=0.2206)	11.9% (4.1 to 19.5; p=0.003)	N/A	N/A

The FAS population included all randomly assigned patients who received at least one dose of study medication. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90kg versus >90kg) and previous exposure to biological therapy for psoriasis with sample size weights. p values were calculated with the CMH test and stratified by bodyweight and exposure to biological therapies; p values were not adjusted for multiplicity. DLQI is calculated relative to observed data. Abbreviations: CI: Confidence Interval; CMH: Cochran-Mantel-Haenszel; DLQI: Dermatology Life Quality Index; N/A: not applicable; OD: observed data. Reich et al 2017 and reSURFACE 2 CSR.[36,38]

The proportion of patients achieving a DLQI score of 0 or 1 increased between Week 12 and Week 28 from 40.2% (119 of 296 patients with data) to 54.1% (157 of 290 patients with data) in subjects who continued on tildrakizumab 100mg throughout Part 2. The corresponding figures for patients continuing on tildrakizumab 200mg

throughout Part 2 were 47.4% (145 / 306 patients with data) to 65.0% (193 / 297 patients with data).

The proportion of patients achieving a DLQI score of 0 or 1 was significantly higher in both the tildrakizumab 100mg group (47.4%) and the tildrakizumab 200mg group (65.0%) than in the etanercept group (39.4%; p<0.001) at Week 28 (Table 20).[36,38]

Table 20: DLQI score of 0 or 1 at Week 28 in Part 2 of reSURFACE 2

DLQI score 0 or 1 (OD)	Tildrakizumab 100mg (N=294)*	Tildrakizumab 200mg (N=299)*	Placebo to tildrakizumab 100mg (N=69)*	Placebo to tildrakizumab 200mg (N=72)*	Etanercept (n=289)*
Subjects with data	290	297	68	69	282
n (%)	157 (54.1%)	193 (65.0%)	26 (38.2%)	39 (56.5%)	111 (39.4%)
% difference from etanercept (95% CI; p value)	15.0% (6.9 to 22.9; p<0.001)	25.7% (17.7 to 33.4; p<0.001)	N/A	N/A	N/A

The FAS population included all patients entering Part 2 who received at least one dose of study medication. Observed data were pre-specified for the DLQI outcome. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90kg versus >90kg) and previous exposure to biological therapy for psoriasis with sample size weights. p values were calculated with the CMH and stratified by bodyweight and exposure to biological therapies; p values were not adjusted for multiplicity. *Numbers shown include participants with missing data. Abbreviations: CMH: Cochran-Mantel-Haenszel; DLQI: Dermatology Life Quality Index; N/A: not applicable; OD: observed data. Source: Reich et al 2017 and reSURFACE 2 CSR.[36,38]

Quality-of-life in Part 3 of the reSURFACE studies: Maintenance of effect

Improvements in DLQI scores were maintained over time in both reSURFACE studies.

In reSURFACE 1:

- [redacted] and [redacted] of patients treated with tildrakizumab 100mg and 200mg, respectively, throughout the study who were PASI 75 responders at Week 28 had a DLQI of 0 or 1 at Week 64 (see Appendix M for further details).[37]

In reSURFACE 2:

- 68.8% [redacted] and 72.4% [redacted] of patients who were PASI responders at Week 28 and who were treated with tildrakizumab 100mg and 200mg, respectively, throughout the study had DLQI of 0 or 1 at Week 52 (see Appendix M for further details).[1,37,38]

EQ-5D: reSURFACE 1

QoL was also assessed using EQ-5D as an exploratory endpoint in reSURFACE 1. EQ-5D index as well as the individual component scores and change from baseline were collected at weeks 12, 28, 40, 52 and 64 (see Appendix M). In the tildrakizumab 100mg and 200mg groups, EQ-5D scores remained consistent and similar over Parts 1 and Part 2 of the study.[37]

B.2.7 Subgroup analysis

Pre-specified subgroup analyses based on the co-primary endpoints were carried out as outlined in the study protocols and as stated in Table 7.[37,38]

- Previous use of biologic therapy for psoriasis
- Body weight (baseline weight ≤90kg and >90kg)

In addition, two post-hoc analyses were carried out to consider the clinical efficacy of tildrakizumab in the following two subgroups outlined in the NICE scope:

- Previous use of phototherapy and systemic non-biological therapy (which includes fumaric acid, methotrexate, methotrexate sodium, ciclosporin, acitretin, calcium monoethyl fumarate (+) dimethyl fumarate (+) magnesium monoethyl fumarate (+) zinc monoethyl fumarate, dimethyl fumarate and apremilast.
- Severity of psoriasis assessed in patients with a baseline PASI <20 and ≥20.

For the pre-specified analyses, treatment differences were provided for each subgroup based on the Miettinen-Nurminen test (stratified by body weight [≤90kg, >90kg] and prior exposure to biologic therapy for psoriasis (yes/no) with sample size weights) with 95% CI comparing each dose of tildrakizumab versus placebo.[37,38]

Forest plots are included in Appendix E along with results of additional pre-specified analyses outlined in the study protocols and as stated in Table 7. Due to the limited sample size in some subgroups and variations in the data within subgroups (i.e. wide CIs), statistical comparisons are limited but there were no material differences between any of the subgroups analysed.[37,38] According to these data tildrakizumab 100mg and 200mg are effective options for patients regardless of prior treatment with systemic biologic or systemic non-biologic therapies including phototherapy.

Subgroups of interest due to anticipated recommendation in European licence for tildrakizumab 200mg

The recommended licensed dose of tildrakizumab is 100mg. However, the licence also includes the option for use of an increased dose in patients with certain characteristics (high disease burden, body weight ≥90kg).

To better identify patients with high disease burden, subpopulation analyses were undertaken for patients in the reSURFACE studies. Results of pooled analyses demonstrate that the parameters with greatest effect on clinical efficacy are baseline PASI score and body weight.

The results of a pre-planned analysis of baseline body weight data show a trend towards better clinical outcomes (PASI and PGA responses) in patients >90kg treated with tildrakizumab 200mg compared to those treated with tildrakizumab 100mg at Week 28 (Figure 16).

In addition results of a post-hoc analysis of baseline severity data also show a trend towards better clinical outcomes with the 200mg dose of tildrakizumab for patients with a high disease burden (defined as a baseline PASI ≥20) compared to those receiving the 100mg tildrakizumab dose at Week 28 (Figure 17).

It should be noted that although the reSURFACE studies were not designed nor powered to detect potential differences between the 100mg and 200mg doses of tildrakizumab, the differences observed via these pre-planned and post-hoc analyses may be clinically relevant.

Figure 16: Efficacy of tildrakizumab at Week 28 by weight (≤90kg, >90kg)

Shows pooled NRI data from the reSURFACE 1 and reSURFACE 2 studies. Numbers are percentages of responders for each efficacy measure. Abbreviations: PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment. Source: Almirall data on file 2018[41]

Figure 17: Efficacy of tildrakizumab at Week 28 by baseline PASI (<20, ≥20)

Shows pooled NRI data from the reSURFACE 1 and reSURFACE 2 studies. Numbers are percentages of responders for each efficacy measure. . Abbreviations: PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment. Source: Almirall data on file 2018[41]

B.2.8 Meta-analysis

A network meta-analysis (NMA) was conducted. This is described in section B.2.9.

B.2.9 Indirect and mixed treatment comparisons

A head to head trial of tildrakizumab against etanercept has been conducted (Section B.2.6.2). To assess the comparative effectiveness of tildrakizumab to the other relevant comparators, a NMA was undertaken.

The NMA was informed by extensive literature searches. Full details of the methodology for the NMA are presented in Appendix D. The literature review and eligibility criteria were designed to identify all RCTs of the relevant comparators in patients with moderate to severe psoriasis. The study selection process is shown in Figure 18.

Forty five studies were identified that contributed to the NMA. All the studies were connected through one or more common treatment arms and included licensed doses of treatments specified in the scope compared against each other, other interventions or placebo. Several of the included studies had multiple arms, often including treatments that are not directly relevant to this submission, because the NMA was conducted on a global basis and therefore considers treatment not used in standard UK clinical practice. In these cases, all treatment arms of the eligible studies were included in the network (including unlicensed doses). The NMA focused on the PASI response rates with the results used to inform the economic model.

The following treatments specified in the NICE scope are included in the NMA:

- Tildrakizumab (100mg or 200mg)
- Adalimumab (40mg Q2W))
- Etanercept (50mg QW, 25mg BIW – data on these two doses were pooled)
- Ixekizumab (80mg Q4W)
- Secukinumab (300mg Q4Q)
- Ustekinumab (45mg, 90mg, 45mg to 90mg Q12W)
- Brodalumab (210mg Q2W)
- Guselkumab (100mg Q8W)

Additional treatments

- Apremilast (30mg)
- Dimethyl fumarate (maximum dose of 240mg three times a day)

Etanercept 25mg twice weekly (BIW) and 50mg weekly (QW) were assumed to have the same clinical efficacy, and were pooled into a single etanercept 50mg per week treatment arm.

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 additional treatments listed above, while not direct comparators from a UK clinical practice perspective, were included in the NMA and their inclusion enables a more complete network to be used for the final health economic assessment.

All studies reported data at the end of a short term treatment period, the length of which varied from 12 to 16 weeks across studies. 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 impact of using different time points a sensitivity analysis was conducted using only 12 week data.

An additional analysis was conducted to assess efficacy at 24 to 28 weeks. This was a reduced network as not all studies reported data at the later time points.

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

Studies are summarised in Table 21 and described in detail in Appendix D. The network diagram is shown in Figure 19.

The NMA was planned in three stages:

Stage I analysis

The outcome for the stage I analysis was PASI response (PASI 50, PASI 75, PASI 90 and PASI 100) at 12-16 weeks. Where a study reported results at more than one time-point within this range, the results at the earliest time-point were used.

Stage II analysis

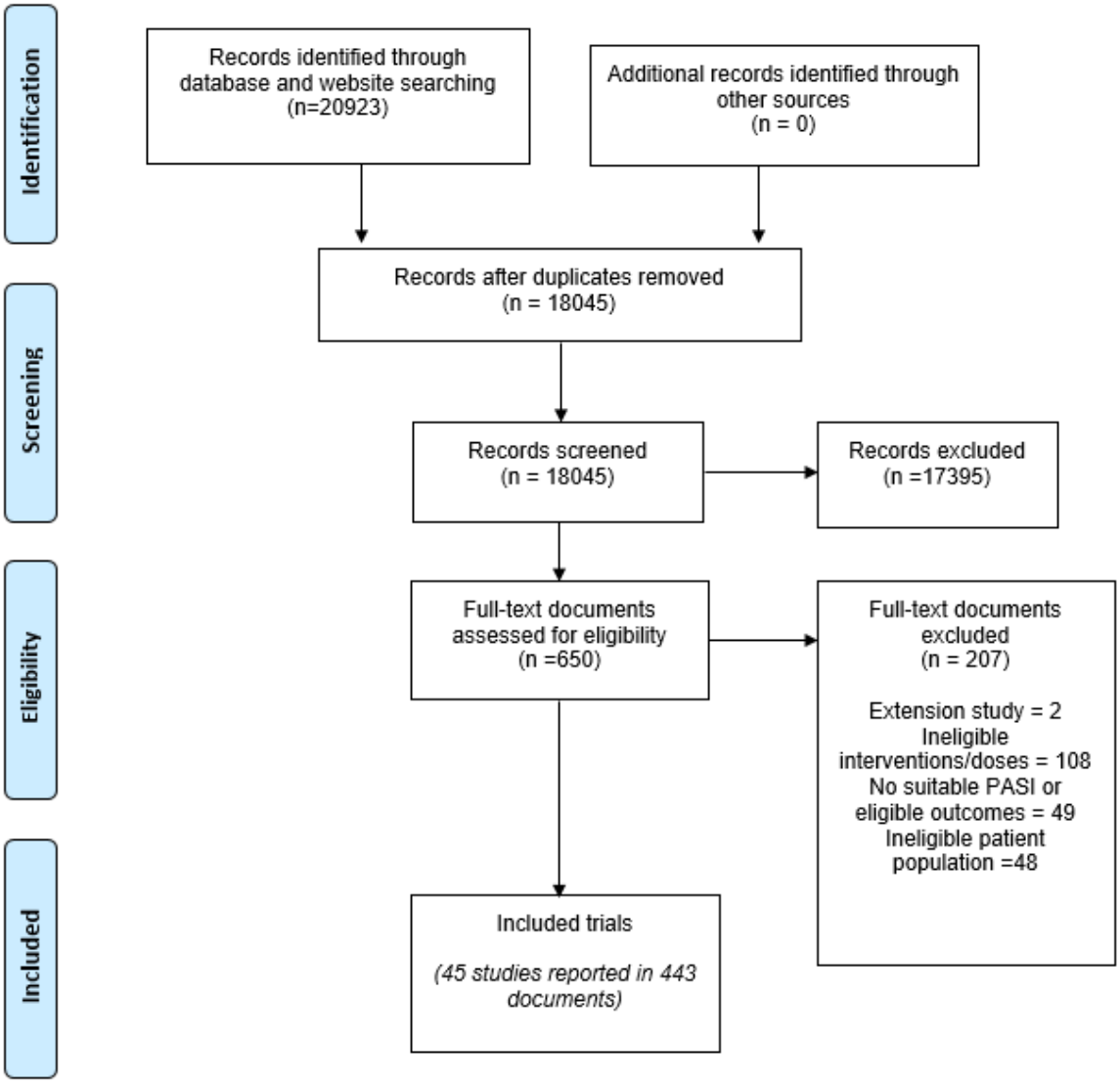
The outcome for the stage II analysis was PASI response (PASI 50, PASI 75, PASI 90 and PASI 100) at 24-28 weeks. Placebo arms were to be removed since this

time-point is after the cross-over in most studies, resulting in a reduced network including only studies with two or more intervention arms.

Stage III analysis

The outcome for the stage III analysis was PASI response (PASI 50, PASI 75, PASI 90 and PASI 100) at 24-28 weeks. Since this point is after the cross-over in most studies, in this analysis the assumption was made that the placebo group results were the same as those at the last time-point before crossover.

Figure 18: PRISMA flow diagram showing record selection process for NMA studies



Abbreviations: PASI: psoriasis area severity index.

Table 21: Summary of all trials used to conduct the NMA

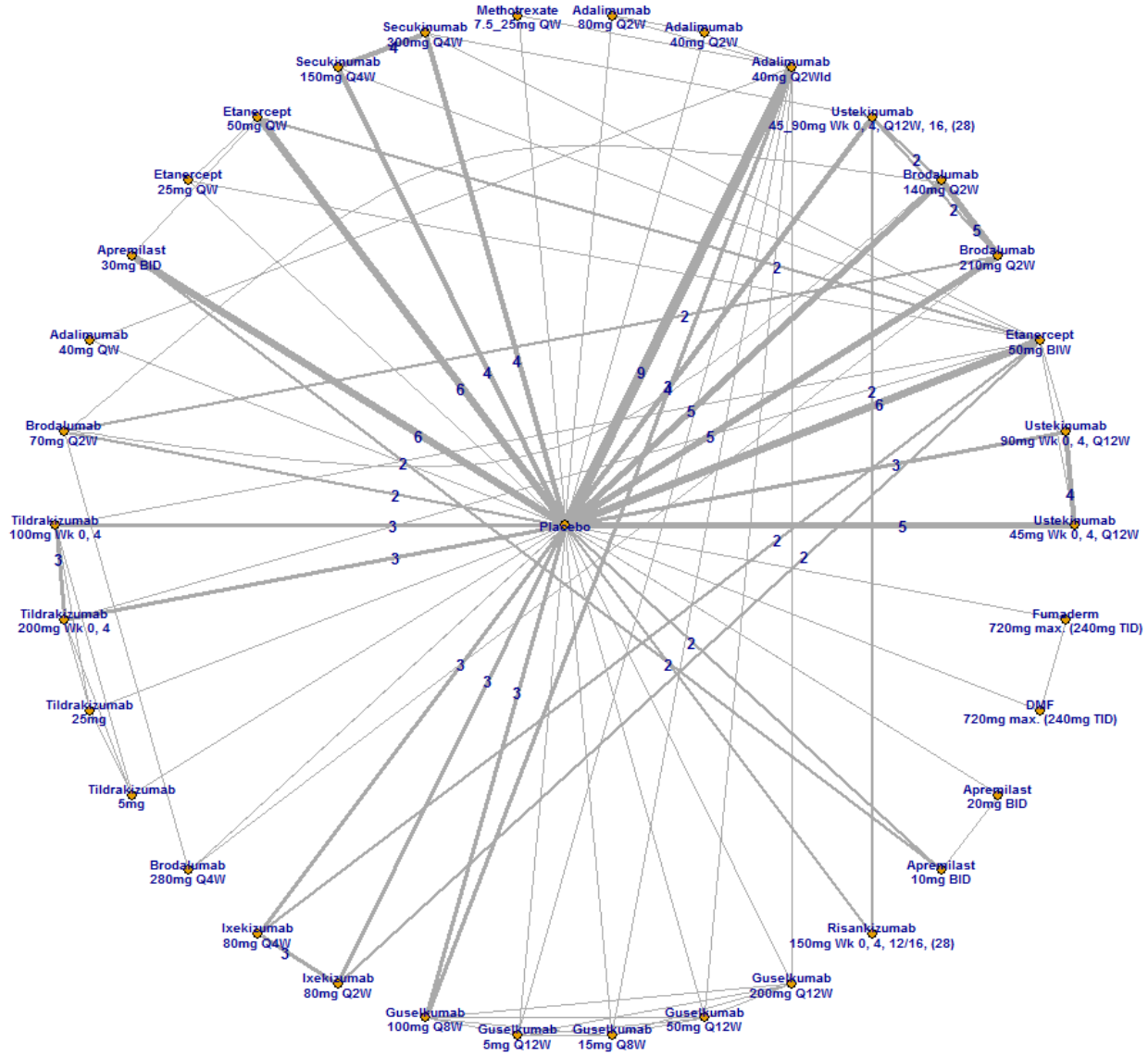
	Intervention						
Trial identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**
ACCEPT[42]	Etanercept 50mg BIW	Ustekinumab 45mg wk 0, 4	Ustekinumab 90mg wk 0, 4				
AMAGINE 1[43]	Placebo	Brodalumab 140mg Q2W	Brodalumab 210mg Q2W				
AMAGINE 2[44]	Placebo	Ustekinumab 45mg/90mg wk 0, 4, Q12W	Brodalumab 140mg Q2W	Brodalumab 210mg Q2W			
AMAGINE 3[45]	Placebo	Ustekinumab 45mg/90mg wk 1, 4, Q12W	Brodalumab 140mg Q2W	Brodalumab 210mg Q2W			
Asahina et al 2010[46]	Placebo	Adalimumab 40mg Q2Wld	Adalimumab 40mg Q2W (no loading dose)	Adalimumab 80mg Q2Wld			
Bissonnette et al 2013[47]	Placebo	Adalimumab 40mg Q2W					
BRIDGE[48]	Placebo	DMF maximum 720mg daily (240mg TID)	Fumaderm maximum 720mg daily (240mg TID)				
CHAMPION[49]	Placebo	Methotrexate 7.5mg to 25mg QW	Adalimumab 40mg Q2W				
CLEAR[50]	Secukinumab 300mg Q4W	Ustekinumab 45mg / 90mg wk 0, 4, Q12W					
CORE[51]	Placebo	Apremilast 30mg BID	Apremilast 10mg BID	Apremilast 20mg BID			
ERASURE[52]	Placebo	Secukinumab 300mg Q4W	Secukinumab 150mg Q4W				
ESTEEM 1[53]	Placebo	Apremilast 30mg BID					
ESTEEM 2[54]	Placebo	Apremilast 30mg BID					
FEATURE[55]	Placebo	Secukinumab 300mg Q4W	Secukinumab 150mg Q4W				

FIXTURE[52]	Placebo	Secukinumab 300mg Q4W	Secukinumab 150mg Q4W	Etanercept 50mg BIW / QW			
Gottlieb et al 2003[56]	Placebo	Etanercept 25mg BIW					
Igarashi et al 2012[57]	Placebo	Ustekinumab 45mg wk 0, 4, Q12W	Ustekinumab 90mg wk 0, 4, Q12W				
JUNCTURE[58]	Placebo	Secukinumab 300mg Q4W	Secukinumab 150mg Q4W				
Leonardi et al 2003[59]	Placebo	Etanercept 25mg QW	Etanercept 25mg BIW	Etanercept 50mg BIW			
LIBERATE[60]	Placebo	Apremilast 30mg BID	Etanercept 50mg QW				
LOTUS[61]	Placebo	Ustekinumab 45mg wk 0, 4					
M02-528[62]	Placebo	Adalimumab 40mg Q2W	Adalimumab 40mg QW				
Nakagawa et al 2016[63]	Placebo	Brodalumab 70mg Q2W	Brodalumab 140mg Q2W	Brodalumab 210mg Q2W			
Ohtsuki 2017[64]	placebo	Apremilast 30mg BID	Apremilast 10mg BID				
Papp 2015 (P05495)[35]	Tildrakizumab 5mg wk 0,4	Tildrakizumab 25mg wk 0,4	Tildrakizumab 100mg wk 0,4	Tildrakizumab 200mg wk 0,4	Placebo		
Papp et al 2005[65]	Placebo	Etanercept 25mg BIW	Etanercept 50mg BIW / 25mg BIW				
Papp et al 2012[66]	Placebo	Brodalumab 70mg Q2W	Brodalumab 140mg Q2W	Brodalumab 210mg Q2W	Brodalumab 280mg Q4W		
PEARL[67]	Placebo	Ustekinumab 45mg wk 0, 4, Q12W					
PHOENIX 1[68]	Placebo	Ustekinumab 45mg wk 0, 4, Q12W	Ustekinumab 90mg wk 0, 4, Q12W				
PHOENIX 2[69]	Placebo	Ustekinumab 45mg wk 0, 4, Q12W	Ustekinumab 90mg wk 0, 4, Q12W				
reSURFACE	Placebo	Tildrakizumab 100mg wk	Tildrakizumab 200mg wk				

1[36]		0,4	0,4				
reSURFACE 2[36]	Placebo	Tildrakizumab 100mg wk 0,4 Q12W	Tildrakizumab 200mg wk 0,4 Q12W	Etanercept 50mg BIW / QW			
REVEAL[70]	Placebo	Adalimumab 40mg Q2W 80mg loading dose					
Trying et al 2006[71]	Placebo	Etanercept 25mg BIW					
ultIMMa-1[72]	Placebo	Risankizumab 150mg wk 0, 4, 16, 28, 40	Ustekinumab 45mg / 90mg Wk 0, 4,16, 28, 40				
ultIMMa-2[72]	Placebo	Risankizumab 150mg wk 0, 4, 16, 28, 40	Ustekinumab 45mg / 90mg wk 0, 4, 16, 28, 40				
UNCOVER 1[73]	Placebo	Ixekizumab 80mg Q4W	Ixekizumab 80mg Q2W				
UNCOVER 2[74]	Placebo	Etanercept 50mg BIW	Ixekizumab 80mg Q4W	Ixekizumab 80mg Q2W			
UNCOVER 3[74]	Placebo	Etanercept 50mg BIW	Ixekizumab 80mg Q4W	Ixekizumab 80mg Q2W			
UNVEIL[75]	Placebo	Apremilast 30mg BID					
Van de Kerkhof et al 2008[76]	Placebo	Etanercept 50mg QW					
VOYAGE 1[77]	Placebo	Guselkumab 100mg wk 0, 4, 12	Adalimumab 40mg Q2W				
VOYAGE 2[78]	Placebo	Adalimumab 80mg at wk 0, 40mg wk1, 40mg Q2W	Guselkumab 100 mg wk 0, 4, 12				
X-PLORE[79]	Placebo	Guselkumab 5mg Q12W	Guselkumab 15mg Q8W	Guselkumab 50mg Q12W	Guselkumab 100mg Q8W	Guselkumab 200mg Q12W	Adalimumab 40mg Q2W
Zhang et al 2015[80]	Placebo	Adalimumab 40mg Q2W					

Abbreviations: BID: twice daily; BIW: twice weekly; ld: loading dose; QW: weekly; Q2W: every two weeks; Q4W: every four weeks; Q8W: every eight weeks; Q12W: every twelve weeks; TID: three times daily; wk: week.

Figure 19: Network diagram



Abbreviations: BID: twice daily; BIW: twice weekly; QW: weekly; Q2W: every two weeks; Q4W: every four weeks; Q8W: every eight weeks; Q12W: every twelve weeks.

The network diagram shows all treatments in any eligible study which were used in the NMA. Some treatments are not a focus for this submission and results for these are not reported below.

Results of the NMA

Underlying assumptions of the analysis are as follows:

- The model described in Appendix D is appropriate.
- It is appropriate to aggregate study results from 12 weeks and 16 weeks.

- It is appropriate to assume that the treatment effects of placebo are constant after Week 16.

The assumptions are further examined in sensitivity analyses. The impact of placebo adjustment has also been examined in a sensitivity analysis, and the results are briefly reported. Note that no analysis of dropout rates has been undertaken.

A list of the trials used to carry out each of the analyses is presented in Appendix L, along with network diagrams and results for each stage of the analysis. WinBUGS codes for the models are shown in Appendix D.

Parameters and convergence measures of the runs are displayed in Appendix L. The WinBUGS parameters used for a given network were re-used for the inconsistency analysis of the same network. In general, convergence was satisfactory, with effective sample sizes of relevant nodes in the hundreds at least, and maximal shrinkage factor (psrf, upper 95% credibility limit) in the worst case at 1.1.

Results for stage I: Weeks 12 / 16

In terms of model fit, the random effects (RE) model has a smaller value for deviance information criterion (DIC), in spite of the number of effective parameters, pD being larger (DIC = 2938.43 and pD = 81.74 for the fixed effect (FE) model, DIC = 2926.79 and pD = 102.90 for the RE model). Therefore, the RE model is preferred over the FE model.

Furthermore, the model calculates risk ratios based on estimated treatment effects using a Bayesian approach. The RE model allows for treatment effects to vary by study, while the FE model does not. Since there is substantial heterogeneity for placebo treatment effects present in the selected studies (I^2 = 67% at PASI 50, I^2 = 53% at PASI 75, I^2 = 13% at PASI 90, and I^2 = 0% at PASI 100), the RE model is more appropriate to account for this.

The results of the RE model suggest that tildrakizumab 100mg is superior to placebo and etanercept 50mg for all examined PASI levels: 50, 75, 90, and 100. [redacted]

[redacted]

The results of the RE model suggest that tildrakizumab 200mg is superior to placebo and etanercept 50mg for all examined PASI levels: 50, 75, 90, and 100. [redacted]

All active treatments were found to be significantly better than placebo at all PASI levels.

Details of risk ratios relative to tildrakizumab 100mg wk 0, 4, tildrakizumab 200mg wk 0, 4 and placebo are illustrated via the forest plots in Figure 20, Figure 21 and Figure 22. The data in Figure 20 and Figure 21 are used to inform the economic model (see Section 3.3)

Figure 20: Risk ratios relative to tildrakizumab 100mg wk 0, 4

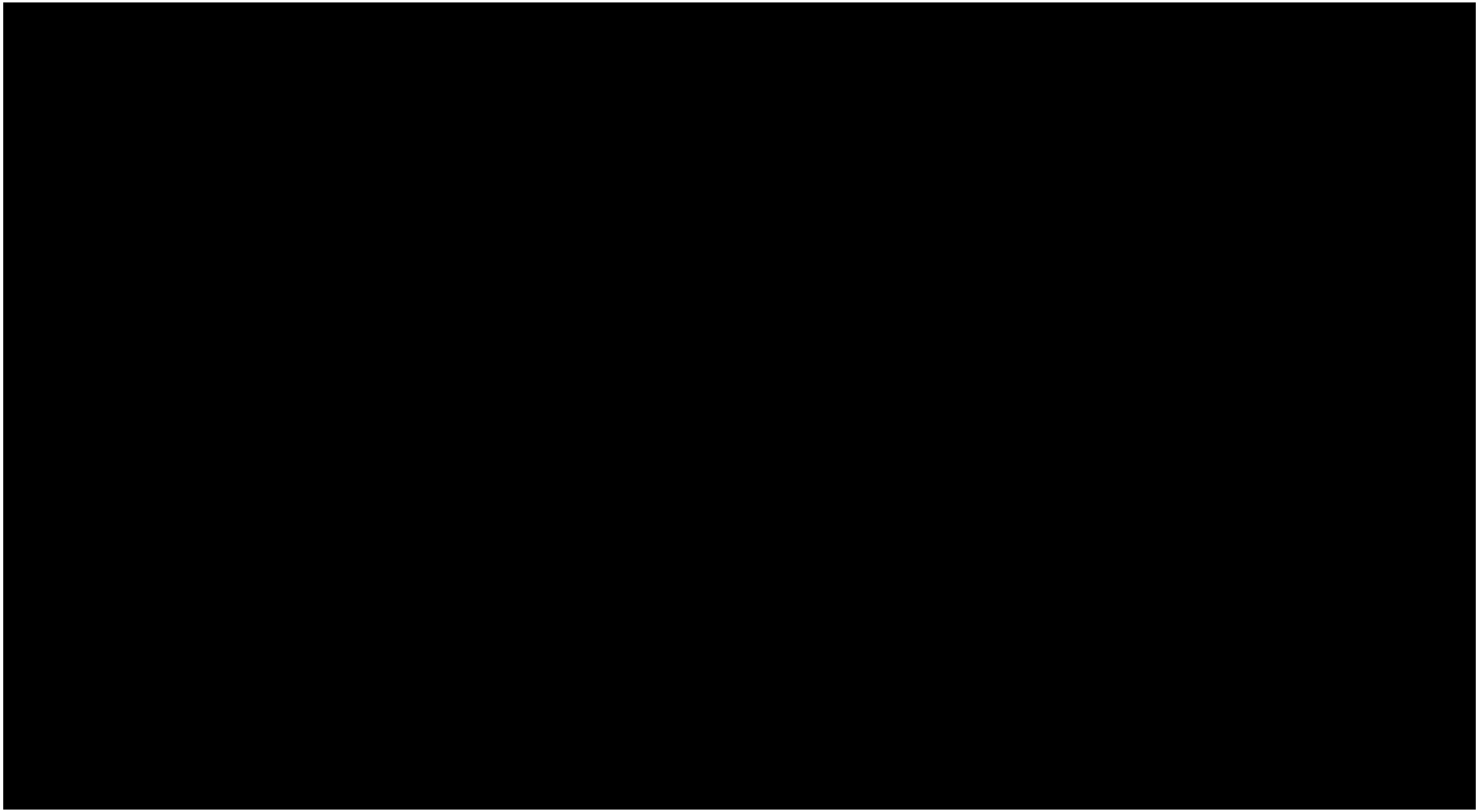


Figure 21: Risk ratios relative to tildrakizumab 200mg wk 0, 4

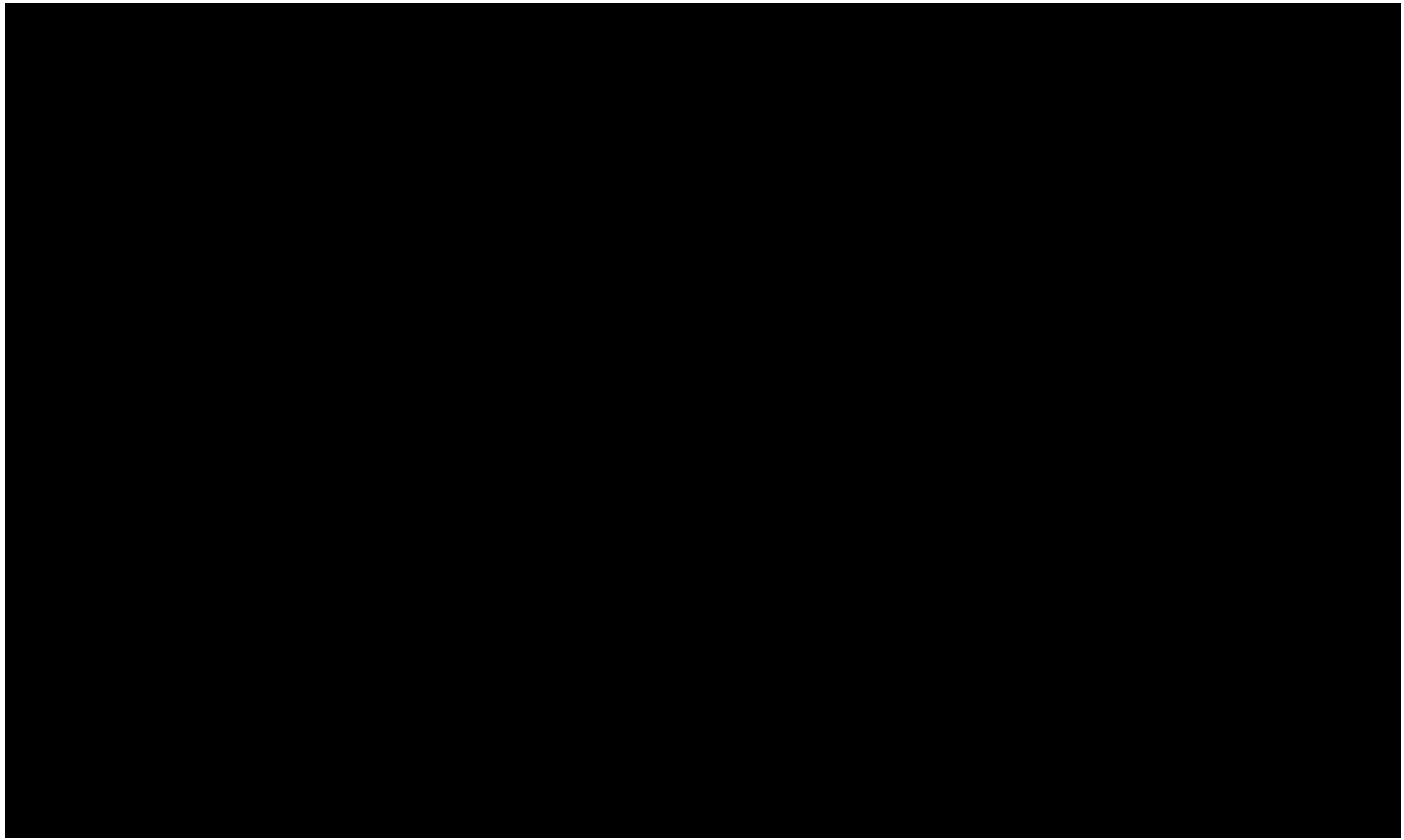
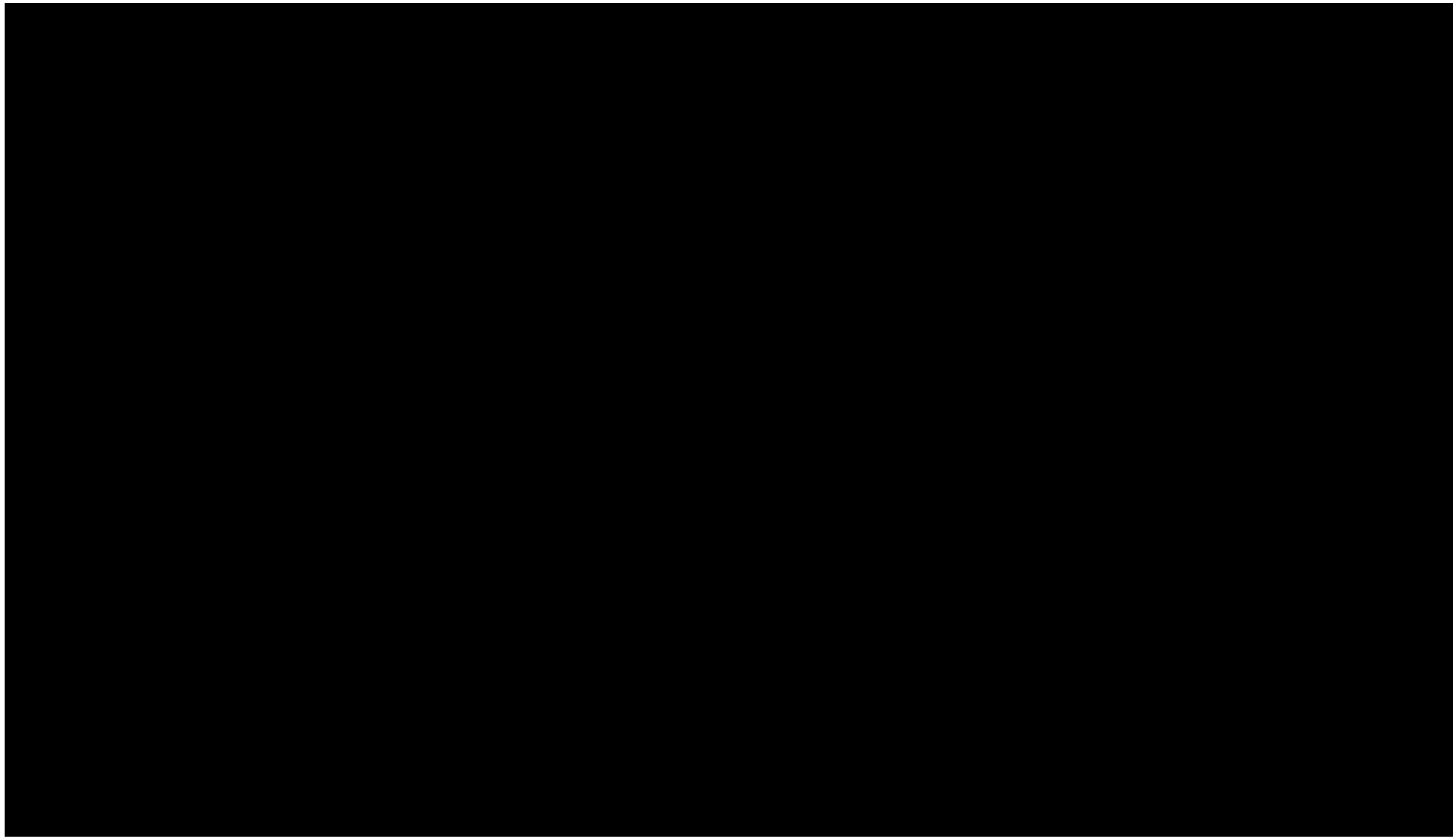


Figure 22: Risk ratios relative to placebo



Estimated risk ratios, treatment effects and Forest plots of treatment effects are shown in Appendix L.

Results of stage I: sensitivity analyses – results

Two sensitivity analyses were undertaken:

- including data from 12 weeks only
- examining the impact of placebo adjustment.

All results regarding "weeks 12 only" are included in Appendix L. The impact of placebo adjustment was assessed and found not to offer any advantages over the model without placebo adjustment (details excluded).

Results of stage II: weeks 24 / 28 without placebo arms

This part of the planned analysis was not possible because once the placebo arms were removed from studies in the weeks 24/28, tildrakizumab was not connected to any other treatment of interest.

Results of stage III: weeks 24/28 with placebo arms

All results regarding stage III are included in Appendix L.

Uncertainties in the indirect and mixed treatment comparisons

Stage I: Weeks 12 / 16 – heterogeneity and inconsistency

No concerns regarding heterogeneity and inconsistency were identified from selecting the RE model. More details can be found in Appendix L.

Stage I: sensitivity analyses – heterogeneity and inconsistency

No concerns were identified regarding cases 'Week 12 only' if selecting the RE model. More details can be found in Appendix L.

Stage III: weeks 24 / 28 with placebo – heterogeneity and inconsistency

No concerns were identified, and details are displayed in Appendix L.

B.2.10 Adverse reactions

Adverse reactions data are presented for a pooled analysis from the Phase IIb and III studies plus adverse event (AE) data from each of the reSURFACE studies.

Summary of adverse events

- Tildrakizumab has demonstrated a favourable safety profile when compared with etanercept and placebo.[81]
- Tildrakizumab is well tolerated, with low rates of serious treatment emergent adverse events (TEAEs), discontinuations due to AEs, and AEs of clinical interest.[81]

Pooled analysis from Phase IIb and Phase III clinical studies

Data from three placebo-controlled studies (one Phase IIb and the two Phase III reSURFACE studies)[35,36] were integrated to assess the safety and tolerability of tildrakizumab.[81] The analysis included 2,081 patients (tildrakizumab 100mg (n=705), tildrakizumab 200mg (n=708), placebo (n=355) or etanercept (n=313):

- In the placebo-controlled period (up to 16 weeks):
    - The frequencies (patients divided by number of patients exposed) of TEAEs for tildrakizumab 100mg, tildrakizumab 200mg, placebo and etanercept were 48.2%, 47.9%, 53.8%, and 54.0%, respectively.[81]
    - Frequencies of 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%); major adverse cardiovascular events (MACEs; range 0.0 to 0.1%) and severe infections (range 0.0 to 0.3%) were comparable between tildrakizumab 100mg, tildrakizumab 200mg, placebo and etanercept.[81]
    - The most common TEAE in all treatment groups was nasopharyngitis.[81]
- In the full trial periods (up to Week 52 for phase IIb and reSURFACE 2, and up to Week 64 for reSURFACE 1):
    - Exposure-adjusted rates (patients per 100 patient-years) for TEAEs, serious TEAEs and discontinuations due to AEs with tildrakizumab were lower than or comparable with the placebo rates, and lower than with etanercept.[81]

- Exposure adjusted rates for TEAEs for tildrakizumab 100mg, tildrakizumab 200mg, placebo and etanercept were 77.0, 79.3, 153.5 and 148.6, respectively (see Table 22).[81]
- Exposure-adjusted rates of MACEs (range 0.0 to 0.5) and severe infections (range 0.9 to 2.0) were comparable among groups.[81]
- No TEAEs of inflammatory bowel disease or suicide were reported.
- Candida skin infections were infrequent with exposure-adjusted rates of 0.2, 0.7, 0.0 and 0.0, for tildrakizumab 100mg, tildrakizumab 200mg, placebo and etanercept respectively. Oral candidiasis was also infrequent.[81]
- Seven deaths were reported during the full trial periods. All were considered unrelated to treatment (investigator and study sponsor assessment).[81]

Table 22: Summary of exposure-adjusted adverse events from the pooled analysis of phase IIb and phase III studies (all patients as treated)

Treatment	Placebo-controlled period, n (%)				Full trial period, exposure-adjusted rate, patients per 100 patient-years (95% CI)			
	Tildrakizumab 100mg	Tildrakizumab 200mg	Placebo	Etanercept 50mg	Tildrakizumab 100mg	Tildrakizumab 200mg	Placebo	Etanercept 50mg
Patients, N	705	708	355	313	1083	1041	588	313
TEAEs	340 (48.2)	339 (47.9)	191 (53.8)	169 (54.0)	77.0 (74.0 to 79.9)	79.3 (76.1 to 82.4)	153.5 (142.5 to164.4)	148.6 (137.8 to 158.5)
Treatment-related AEs	104 (14.8)	99 (14.0)	47 (13.2)	92 (29.4)	23.3 (20.7 to 26.1)	25.2 (22.4 to 28.2)	37.9 (30.6 to 46.2)	73.0 (62.2 to 84.4)
Serious AEs	10 (1.4)	16 (2.3)	6 (1.7)	7 (2.2)	5.8 (4.4 to 7.5)	7.2 (5.6 to 9.1)	6.4 (3.5 to 10.6)	13.0 (8.1 to 19.8)
Treatment-related serious AEs	0	3 (0.4)	0	2 (0.6)	0.3 (0.1 to 0.9)	1.0 (0.4 to 1.8)	0.9 (0.1 to 3.3)	3.3 (1.1 to 7.5)
Discontinued due to TEAEs	4 (0.6)	9 (1.3)	4 (1.1)	6 (1.9)	2.2 (1.4 to 3.3)	2.2 (1.3 to 3.3)	2.3 (0.7 to 5.3)	5.9 (2.7 to 11.0)
Discontinued due to treatment-related AEs	1 (0.1)	3 (0.4)	2 (0.6)	4 (1.3)	0.8 (0.3 to 1.6)	0.9 (0.4 to 1.7)	0.9 (0.1 to 3.3)	2.6 (0.7 to 6.6)

Abbreviations: AE: adverse event; CI: confidence interval; TEAE: treatment-emergent AE. Source: Blauvelt et al 2018.[81]

Analysis from reSURFACE 1 and 2 phase III studies

- Discontinuation due to AEs was infrequent in patients taking tildrakizumab 100mg and 200mg (≤2% across all Parts of the reSURFACE 1 and 2 studies).
- Serious AEs were rare and were consistent across study groups.
- The incidence of severe infections, malignancies and MACEs were low and were similar across treatment groups.
- Treatment with tildrakizumab was associated with a low incidence of injection site reactions. Injection site reactions occurred in [redacted] of patients taking tildrakizumab 100mg and 200mg across all parts of reSURFACE 1.[37] In Part 1 of reSURFACE 2, injection site reactions occurred in 5% of patients treated with etanercept, whereas they were infrequent (≤1%) for tildrakizumab 100mg and 200mg treated patients during both Parts 1 and Parts 2 of the study (Table 23, Table 24).[36-38]
- Tildrakizumab was associated with low immunogenicity in the reSURFACE studies (see following section). There was no apparent association between the development of antibodies to tildrakizumab and the development of TEAEs.
- Malignancies consisted mostly of non-melanoma skin cancer; no patients had melanoma skin cancer (Table 23, Table 24).[36-38]
- Candida infections were infrequent in patients taking tildrakizumab in the reSURFACE studies (<1% in all parts of reSURFACE 1 and 2), suggesting that interleukin 23p19 neutralisation with tildrakizumab is not associated with a risk of fungal infection.[36-38]
- Previous evidence suggests that targeting of interleukin 23 is therapeutic in IBD, whereas neutralisation of interleukins 17A or 17RA has either no effect or exacerbates the disease.[36] No cases of new-onset IBD or exacerbations of pre-existing disease were reported in the reSURFACE studies, although the number of patients with IBD at baseline was low in both studies.[36-38]

Additional information on AEs reported during each part of the reSURFACE studies is included in Appendix F and details are also provided in the draft Summary of Product Characteristics.[1]

Table 23: Summary of adverse events in reSURFACE 1

	Part 1			Part 2		Part 3	
	Placebo N=154	Tildrakizumab 100mg N=309	Tildrakizumab 200mg N=308	Tildrakizumab 100mg N=374‖	Tildrakizumab 200mg‖ N=370	Tildrakizumab 100mg N=316	Tildrakizumab 200mg N=360
One or more adverse events*	74 (48%)	146 (47%)	130 (42%)	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious adverse events	1 (1%)	5 (2%)	8 (3%)	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to adverse events	1 (1%)	0	5 (2%)	[redacted]	[redacted]	[redacted]	[redacted]
Most common adverse events							
Nasopharyngitis	8 (5%)	24 (8%)	20 (6%)	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	9 (6%)	10 (3%)	15 (5%)	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events of special interest							
Severe infections†	0	1 (<1%)	1 (<1%)	[redacted]	[redacted]	[redacted]	[redacted]
Malignancies‡	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Non-melanoma skin cancer	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Confirmed extended major adverse cardiovascular events§	0	1 (<1%)	1 (<1%)	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related hypersensitivity reactions	0	0	1 (<1%)	[redacted]	[redacted]	[redacted]	[redacted]

Data are n (%).*Participants who took at least one dose of study drug based on the treatment actually received in Parts 1, 2 and 3; in Part 3 includes patients re-randomised to placebo. †Infection meeting the regulatory definition of a serious adverse event, or any infection requiring intravenous antibiotics, irrespective of whether it was reported as a serious adverse event, as per the regulatory definition. ‡Excluding carcinoma in situ of the cervix. §Includes non-fatal myocardial infarction, non-fatal stroke, unstable angina, coronary revascularisation and cardiovascular deaths that are confirmed as 'cardiovascular' or 'sudden'. ‖Includes placebo subjects re-randomised at Week 12 to receive tildrakizumab 100mg and 200mg. Note: [redacted] subjects who were randomised to tildrakizumab 100mg in Part 1 and re-randomized to placebo in Part 3 had an adverse event while they took placebo. [redacted] subjects who were randomised to tildrakizumab 200mg in Part 1 and re-randomised to placebo in Part 3 had an adverse event while they took placebo and [redacted] subjects had a Tier 1 adverse event while they took placebo. One subjects in the tildrakizumab 200mg group had adverse events reported as serious adverse events during Part 3 that should have been reported as non-serious adverse events. Source: Reich et al 2017 and reSURFACE 1 CSR.[36,37]

Table 24: Summary of adverse events in reSURFACE 2

	Part 1				Part 2			Part 3	
	Placebo N=156	Etanercept N=313	Tildrakizumab 100mg N=307	Tildrakizumab 200mg N=314	Tildrakizumab 100mg N=363	Tildrakizumab 200mg‖ N=371	Etanercept N=289	Tildrakizumab 100mg N=410	Tildrakizumab 200mg N=380
One or more adverse events*	86 (55%)	169 (54%)	136 (44%)	155 (49%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious adverse events	4 (3%)	7 (2%)	4 (1%)	6 (2%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	0	0	1 (<1%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to adverse events	2 (1%)	6 (2%)	3 (1%)	3 (1%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common adverse events									
Injection site reaction	1 (1%)	14 (5%)	1 (<1%)	2 (1%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	12 (8%)	36 (12%)	41 (13%)	35 (11%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events of special interest									
Severe infections†	1 (1%)	0	0	1 (<1%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malignancies‡	0	1 (<1%)	1(<1%)	1 (<1%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-melanoma skin cancer	0	1 (<1%)	1(<1%)	1 (<1%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Confirmed extended major adverse cardiovascular events§	0	1 (<1%)	0	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related hypersensitivity reactions	1 (1%)	0	1 (<1%)	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data are n (%).*Participants who took at least one dose of study drug based on the treatment actually received in Parts 1, 2 and 3; in Part 3 includes patients re-randomised to placebo. †Infection meeting the regulatory definition of a serious adverse event, or any infection requiring intravenous antibiotics, irrespective of whether it was reported as a serious adverse event, as per the regulatory definition. ‡Excluding carcinoma in situ of the cervix. §Includes non-fatal myocardial infarction, non-fatal stroke, unstable angina, coronary revascularisation and cardiovascular deaths that are confirmed as 'cardiovascular' or 'sudden'. ‖Includes placebo subjects re-randomised at Week 12 to receive tildrakizumab 100mg and 200mg. Source: Reich et al 2017 and reSURFACE 2 CSR.[36-38]

Immunogenicity

In the pooled Phase IIb and Phase III analyses, 7.3% of tildrakizumab-treated patients developed antibodies to tildrakizumab. No apparent association between the development of antibodies to tildrakizumab and the development of TEAEs was observed.[1]

Studies reporting additional adverse reactions

Appendix F provides brief details of the AEs reported for the one Phase IIb study included in the pooled safety data referred to above that were not included in section 2.2.

B.2.11 Ongoing studies

The optional long-term safety extension studies from the reSURFACE pivotal studies are ongoing: reSURFACE 1 (NCT01722331)[82] and reSURFACE 2 (NCT01729754)[83] with estimated completion dates in 2019.

The effect of tildrakizumab is also being studied in other new indications:

A long term study on the safety and efficacy of tildrakizumab in patients with Psoriatic Arthritis and Ankylosing Spondylitis or Non-Radiographic Axial Spondyloarthritis. (NCT03552276) (estimated completion in 2022).[84]

The manufacturer plans to participate in national registries as soon as tildrakizumab is marketed for psoriasis.

B.2.12 Innovation

Tildrakizumab offers an effective and well tolerated alternative systemic biological therapy for the treatment of moderate to severe plaque psoriasis, for long term use. It is an innovative high-affinity anti IL-23p19 monoclonal antibody, which offers the potential for improved targeting when compared with dual inhibition of both IL-12 and IL23.[1]

The low frequency of maintenance dosing (every 12 weeks) offers a convenient dosing regime that can help meet the needs of patients seeking to minimise disruption to daily life.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Principal findings from the clinical evidence for tildrakizumab

Tildrakizumab provides long term clinical efficacy with a convenient dosing schedule

Tildrakizumab has demonstrated improved clinical efficacy compared to placebo in two pivotal Phase III clinical studies (reSURFACE 1 and 2), and compared to etanercept (reSURFACE 2). A significantly greater number of tildrakizumab treated patients achieved PASI 75, PASI 90, PASI 100 responses at 12 weeks (after only two doses of tildrakizumab 200mg) compared with patients in the placebo groups in both reSURFACE studies and compared to patients in the etanercept group in reSURFACE 2.[36-38]

The efficacy of tildrakizumab continues to increase beyond the primary endpoint between Weeks 12 and 28 with only one additional dose.

Tildrakizumab maintains clinical efficacy over time in patients who achieved a PASI 75 response at Week 28. Pooled data from reSURFACE 1 and reSURFACE 2 long term extension studies showed that efficacy is maintained for up to three years.[1] It is known that drug survival is relatively poor in patients with psoriasis and there is often a need to switch therapy to maintain a response.[28,30] The durability of response with tildrakizumab has the potential to reduce the need to switch therapy, thereby avoiding the associated resource and cost implications for the health service[85,86] and providing more budget certainty for payers.

No clinically relevant differences in efficacy were observed across the pre-specified subgroup analyses carried out for PASI 75 and PGA ‘clear’ or ‘minimal’ responses at Week 12 in both reSURFACE 1 and reSURFACE 2.[36-38] This provides support for the predictability of response with tildrakizumab.

In addition results of a post-hoc analysis of baseline severity data also show a trend towards better clinical outcomes with the 200mg dose of tildrakizumab for patients with a high disease burden (defined as a baseline PASI ≥20) compared to those receiving the 100mg tildrakizumab dose at Week 28. By having two doses, clinicians

are able to choose the most appropriate dose for each patient based on patient characteristics. Clinical experts have commented that dose flexibility with tildrakizumab would be an important consideration[87] because at the moment there is only one other biologic for psoriasis which allows dose adjustment based on patient characteristics.

Tildrakizumab has a favourable safety profile

Tildrakizumab has demonstrated a favourable safety profile when compared with etanercept and placebo.[36-38]

Discontinuation due to AEs was low in patients treated with tildrakizumab (≤2% across all parts of reSURFACE 1 and reSURFACE 2).[36-38] A real-world retrospective study considering treatment with adalimumab, etanercept, infliximab and ustekinumab, demonstrated that AEs associated with withdrawal occurred in 4% of all administered biologic therapies,[88] while another observational cohort study investigating the same therapies, which utilised data from the British Association of Dermatologists Biologic Interventions Register (BADBIR), indicated that 6% of discontinuations in the first year were due to AEs.[30] The rate of discontinuation due to AEs in tildrakizumab treated patients therefore appears favourable in relation to other commonly used biological therapies for psoriasis.

In the pivotal Phase III reSURFACE studies serious AEs were rare with tildrakizumab, as were AEs of special interest including severe infections, malignancies and major adverse cardiovascular events.[36-38]

Infection is the main AE leading to discontinuation with biologic treatments, and serious infections are associated with significant morbidity or mortality.[89] The IL-23 – IL-17 inflammatory pathway not only mediates autoimmune pathology, but is also important for resistance to infection.[36] Specific targeting via selective IL-23p19 inhibition has been developed with the aim of minimising the risk of infection whilst providing effective control of psoriasis. In the reSURFACE studies infections were less frequent or comparable to etanercept and placebo, respectively.[36-38]

Candida infections were infrequent (<1%) in the reSURFACE studies,[36] suggesting that interleukin 23p19 neutralisation with tildrakizumab is not associated with the same risk of fungal infection as anti-interleukin 17 antibodies.[90]

Neutralisation of interleukins 17A or 17RA has either no effect or exacerbates IBD. Tildrakizumab did not induce or exacerbate IBD in the reSURFACE studies.[36] Previous evidence suggests that targeting interleukin 23 may be therapeutic in IBD[36] and further research would be helpful to better characterise the effect of selective neutralisation of interleukin 23 on IBD.

Injection site reactions following subcutaneous administration of biologics have been reported in 13 to 18% of patients with moderate-to-severe plaque psoriasis.[91,92] Such reactions have been reported to be the most common AE associated with etanercept, adalimumab and ixekizumab. The high incidence of injection site reactions during therapy with these products is likely to reflect the administration frequency.[91,92]Treatment with tildrakizumab administered every 12 weeks is associated with a low incidence (<1%) of injection site reactions.[36,38]

Strengths and limitations of the clinical evidence for tildrakizumab

Internal validity

The methodological quality of the reSURFACE studies indicated a low risk of bias during the initial randomised periods of the studies. No assessment has been made during the extension phases, which were not randomised.

There were a number of limitations in the design of the studies:[36-38]

- The study design did not enable long term statistical comparisons with placebo or etanercept for clinical efficacy as there is no placebo controlled period beyond 12 weeks. In reSURFACE 2, etanercept was only continued until Week 28 when patients either discontinued or were re-randomised to tildrakizumab. The reSURFACE studies provide long term safety data for tildrakizumab but comparisons with placebo and etanercept safety data were only possible descriptively as no statistical comparisons were made between the treatment groups.

- Tildrakizumab non-responders were discontinued from both studies at Week 28, whereas for etanercept, at the same timepoint patients who had responded in reSURFACE 2 were discontinued at this 28 week time point. In clinical practice etanercept responders are more likely to continue therapy.
- Data handling:
    - Responders at Week 28 are treated differently in the two studies. This introduces challenges when comparing the results of the two reSURFACE studies beyond week 28.
    - Owing to variability in the handling of missing data as specified in the study protocols, care is needed interpreting results especially at later time points when only observed data are available and patient numbers smaller.
- Depending on the reasons for treatment discontinuation and the number of discontinuations in each treatment arm, there is the potential for the treatment arms to become unbalanced and bias to be introduced. In the reSURFACE studies, although there were differences in discontinuation rates between groups during the individual parts of the studies, the number of patients discontinuing was low and the reasons for discontinuation were similar across groups. As such it was assessed that treatment discontinuation was unlikely to affect outcomes.

External validity

Active comparator: etanercept

Etanercept was the standard of care at the time the reSURFACE studies were designed.[93] Newer biological therapies are now used more frequently and are likely to better represent current standard of care. However, etanercept has a favourable safety profile and clinicians in the UK have wide experience of using etanercept for the treatment of psoriasis in addition to use in other licensed indications. The clinical evidence base combined with the introduction of biosimilars means that the drug remains a relevant treatment today. In the absence of head-to-head data comparing tildrakizumab with the newer (and more effective) biological therapies a NMA was conducted to provide comparisons of efficacy with other biological treatment options outlined in the NICE psoriasis pathway.[16]

The etanercept dose used in reSURFACE 2 was the highest recommended dose (50mg twice weekly for the first 12 weeks, followed by 50mg once a week).[94] Tildrakizumab was shown to be more efficacious than this maximum dose at Week 12 and Week 28 in reSURFACE 2.[36,38] It is likely that if tildrakizumab was compared with the lower dose of etanercept which is routinely used in clinical practice, the difference in efficacy would be more pronounced.

Clinical outcomes

The two main outcome measures evaluated in the reSURFACE studies (PASI and PGA) are consistent with the outcomes assessed in clinical studies for comparator products, are validated and reflect clinical measures of response used in UK clinical practice.[2,26,95]

Trial population

Clinical experts consulted considered that the baseline populations of patients with plaque psoriasis included in the reSURFACE studies are reflective of the population likely to receive tildrakizumab in routine clinical practice in the UK.[87]

Tildrakizumab efficacy

Tildrakizumab is a clinically effective option for the treatment of patients with plaque psoriasis regardless of their previous exposure to other biologic therapies. This will be important in clinical practice where the sequence of therapies used within the treatment pathway is likely to reflect individual patient factors.

In patients on tildrakizumab who maintained treatment until Week 28, PASI 75 and PGA responses continued to improve beyond Week 12, suggesting that the 12 week time point chosen for assessment of the primary efficacy endpoints was too early to adequately assess the full efficacy potential of tildrakizumab in clinical practice. It is suggested that given the improvements in efficacy after the third dose (between Week 16 and Week 28), the most appropriate stopping-rule applicable to tildrakizumab once licensed should be 28 weeks.

Tildrakizumab administration

Tildrakizumab will not require an intense initial loading dose in clinical practice[1] which may reduce the likelihood of injection site reactions.

The low frequency of maintenance dosing for tildrakizumab (of one injection per 12 weeks) is an important option.[1] With the exception of ustekinumab[96] all other biologic therapies require more frequent dosing. Treatment effectiveness and convenience of therapy are both important contributors to patient satisfaction in psoriasis patients. Patient satisfaction has been shown to predict adherence and tildrakizumab's enhanced convenience may impact adherence and ultimately positively affect its effectiveness in clinical practice.[97,98]

Tildrakizumab therapy may be self-administered at home or in the community to improve patient convenience and reduce the need for travel to clinic and take time off work. This is important for psoriasis patients who often report that psoriasis and its treatment has a significant impact on their ability to gain employment or causes them to regularly miss work.[14,29,98,99]

End of life treatment

Tildrakizumab is not considered to be a 'life-extending treatment at the end of life'.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A SLR was conducted to identify evidence to support the development of a cost-effectiveness model for tildrakizumab for moderate to severe plaque psoriasis. A single review was performed to identify relevant studies in plaque psoriasis that included published economic evaluations of tildrakizumab.

Full details of the search strategy and results of the economic SLR are presented in Appendix G.

The outputs from the SLR indicate there have been no previous studies examining the cost-effectiveness of tildrakizumab and therefore a *de novo* health economic analysis was conducted for the purposes of this appraisal.

B.3.2 Economic analysis

Patient population

The anticipated indication for tildrakizumab, as stated in Section B.1.2 is for the treatment of moderate to severe plaque psoriasis. While this population includes patients who would be eligible for conventional systemic therapies (i.e. non-biologic therapies), it is anticipated that in England and Wales tildrakizumab will only be used in the population that are currently eligible for biologic plaque psoriasis therapies. This is limited to those who have a baseline PASI score ≥10 and a DLQI score >10 and have previously failed, or are contraindicated to, conventional systemic therapies. The population is not limited to those who are biologic-naïve, but within the model tildrakizumab is modelled as a first line biologic therapy. This population aligns with all previous biologic therapies that have been appraised by NICE in this indication (i.e. TA103, TA146, TA180, TA350, TA442, TA511 and TA521).[18-23,25]

It should be noted that in the two pivotal phase III studies of tildrakizumab (reSURFACE 1 and reSURFACE 2), at enrolment patients had no minimum requirement for DLQI score whilst they were required to have a baseline PASI score ≥12 (see Section B.2.3).[36] This deviates slightly from the population defined above but is consistent with most recent clinical studies of biologic therapies for psoriasis.

Model structure

A treatment sequence Markov model was developed in Microsoft Excel®, with the overall structure shown in Figure 23, in order to undertake a cost-utility analysis of tildrakizumab versus all relevant comparators.

The key features of the economic model are summarised in Table 25, which also compares the model to the approach adopted for previous NICE appraisals in this indication.

This choice of model structure is consistent with all previous submissions to NICE relating the moderate to severe plaque psoriasis.

Within the model, patients can receive a total of four separate treatments, including three active biologic interventions and BSC, which is always the last option. The time

on each intervention, excluding BSC, is separated into two distinct phases: induction and maintenance. The model consists of four health states (PASI <50, PASI 50 to 74, PASI 75 to 90, PASI >90), as defined by the response to the administered treatment, with these states impacting on a patient's health-related QoL (HRQoL).

For the economic model, and in line with previous appraisals, all treatments are assumed to have an induction period which is used to establish whether patients have responded to treatment.

Patients enter the model and receive the first treatment in the sequence. At the end of the first cycle patients are assigned to one of the four health states, dependent on their PASI response and this constitutes the induction period. Those with a PASI score of 75 or greater remain on treatment and move into the maintenance period in between the first and second cycles. These patients continue to receive the treatment during this maintenance period and are assumed to remain in the health state they were assigned to in cycle one (i.e. PASI 75 to 90 or PASI >90) until they discontinue in a future cycle (discontinuation discussed further below).

For patients with a PASI score of less than 75 during the induction period their response to treatment is deemed to be inadequate and, therefore, they move onto the second treatment in the sequence. The same process is then followed (i.e. patients are assigned to one of four health states based on their response to that treatment with those who respond [PASI ≥75] moving into the maintenance period and those who don't respond moving onto the next treatment) for the second treatment in the sequence, once they had discontinued from this intervention, repeated again for the third and final active treatment. Finally, once patients have discontinued from this third treatment they move onto BSC, which patients are assumed to remain on until their death.

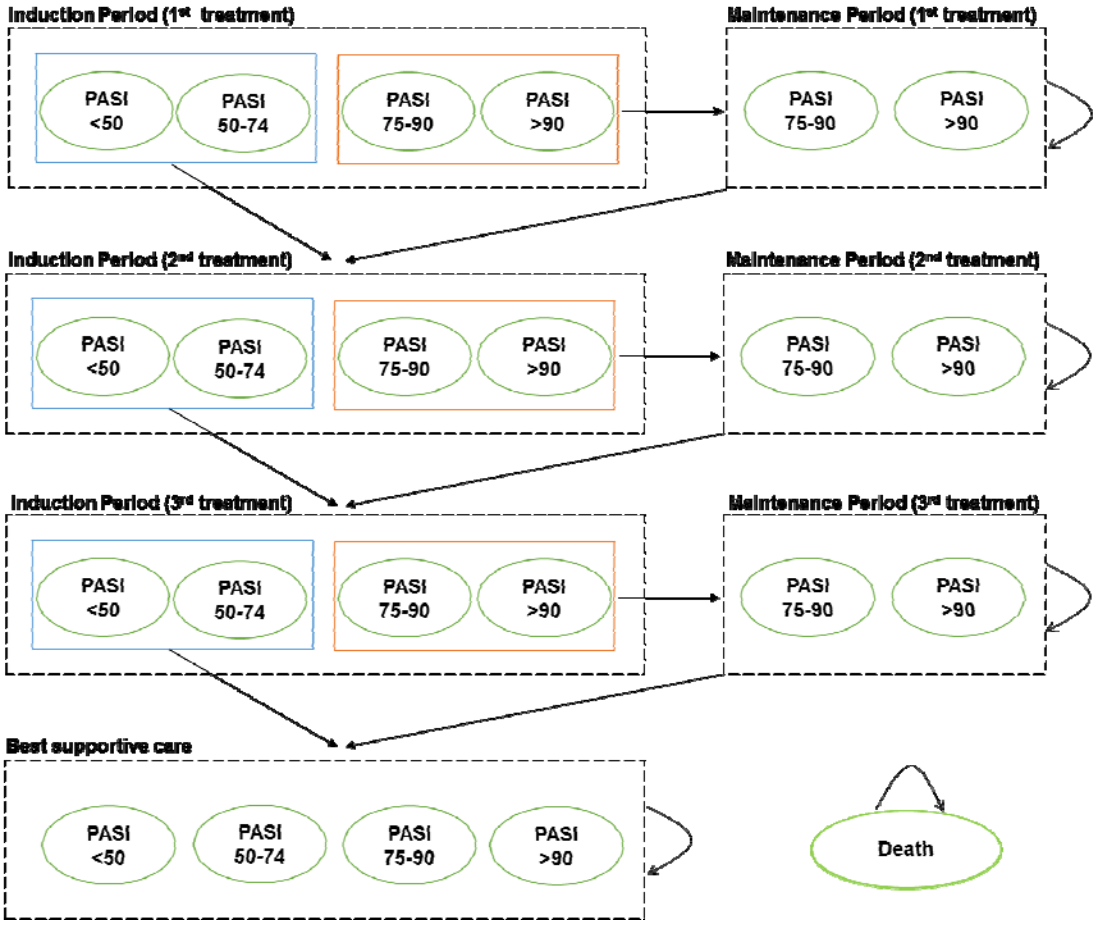
Patients can enter the death state at any cycle in the model, based on age-dependent mortality rates for the general population (i.e. mortality is independent of the treatment in the sequence and health state).

The model was constructed from the perspective of the NHS and Personal and Social Services (PSS) in England and Wales. Fourteen-week cycles were used to

account for the induction period for moderate to severe plaque psoriasis treatments. Generally, this period lasts for between 12 to 16 weeks (summarised in Table 26). Therefore, to simplify the model structure the midpoint of this range was chosen. Also, to reflect the possibility that patients may respond to treatment at any point in the cycle (i.e. not specifically at the end of each cycle during the induction period) a half cycle correction has been applied.

A lifetime horizon was adopted to capture all relevant costs and health-related utilities with all costs and utilities discounted at a rate of 3.5% per year in alignment with the NICE guide to the methods of technology appraisal.[34]

Figure 23: Schematic representation of treatment sequence Markov model



Abbreviations: PASI: psoriasis area severity index.

Table 25: Features of the economic analysis

Factor	Previous appraisals (TA103, TA146, TA180, TA350, TA442, TA511)[18-23]	Current appraisal	
		Chosen values	Justification
Model structure	TA103, TA146, TA180 and TA 350: Decision tree and Markov Model; TA442 and TA511: Markov model	Markov model	The model structure allows for sequencing of treatments over an extended time horizon and also captures the impact of distinct PASI responses on patient HRQoL
Time horizon	Variable: TA103, TA146, TA180 and TA350: 10 years; TA511: 40 years; TA442: lifetime horizon	Lifetime	Adopted to capture all relevant costs and health-related utilities
Cycle length	Variable: TA103, TA146 and TA350: 12 months; TA180: 3 months; TA442: 1 month; TA511: 2 weeks	14 weeks	This cycle length was adopted to account for the induction period for moderate to severe plaque psoriasis treatments
Source of utilities	• TA103: analysis of patient-level data from 3 ETA RCTs and a regression analysis of EQ-5D and DLQI from the Health Outcomes Data Repository (HODaR) database • TA146: mixed model with repeated measures analysis of covariance from two adalimumab RCTs assessing the relationship between changes in EQ-5D, PASI response level and baseline DLQI • TA180: analysis of patient-level data from two ustekinumab RCTs and a regression analysis of EQ-5D and DLQI from the HODaR database • TA350: mixed effects regression model of 5 secukinumab RCTs assessing the relationship between change in EQ-5D, PASI response level and baseline DLQI • TA442: least squares regression model of three ixekizumab RCTs assessing the relationship between change in EQ-5D-5L, PASI response level and baseline EQ-5D-5L. • TA511: least squares regression model of AMAGINE-1 assessed relationship between change in EQ-5D, PASI response level and baseline DLQI	Patient level EQ-5D data from tildrakizumab reSURFACE trials used to generate values by PASI response for patients with DLQI >10	This aligns with previous appraisals in this indication and the adoption of EQ-5D data is also consistent with the NICE reference case. Adoption of data from previous appraisals examined via a scenario analysis
Source of costs	All appraisals: NHS reference costs and PSSRU. In addition: TA103, TA146, TA180 and TA350: BNF; TA 442 and TA511: MIMS	NHS reference costs, PSSRU, BNF	Consistent with the NICE reference case

Treatment waning	In all appraisals treatment effect was assumed to be maintained with ongoing treatment. In all appraisals treatment efficacy was assumed to be the same regardless of exposure to prior therapies	No treatment waning effect modelled	Consistent with all previous NICE appraisals and also necessary given a paucity of data to model a waning effect for all interventions included in the analysis
Treatment-related adverse events (TRAE, grade III/IV)	TA103, TA146 and TA180: not included TA350: impact of TRAEs (NMSC, malignancies other than NMSC, severe infections) on costs included TA442: impact of TRAEs (NMSC, malignancies other than NMSC, severe infections) on costs included in scenario analysis only TA511: impact of serious infections on costs and benefits included in base-case analysis; impact of NMSC, malignancies other than NMSC and MACE on costs included in scenario analysis	Not included	Consistent with a number of previous appraisals in this indication. Furthermore, biologic therapies are well tolerated in this indication and, therefore, adverse events are not a key driver of cost-effectiveness
Mortality	TA103, TA146, TA180, TA350 and TA442: general population mortality included. TA511: general population mortality included and adjusted to account for higher mortality rate for people with severe plaque psoriasis	General population mortality with no adjustment	Consistent with majority of previous appraisals. Higher mortality due to psoriasis modelled as a scenario analysis

Abbreviations: BNF: British National Formulary; DLQI: Dermatology Life Quality Index; EQ-5D: EuroQol five dimension scale; ETA: etanercept; HODaR: Health Outcomes *Data* Repository; HRQoL: health-related quality-of-life; MACE: major adverse cardiovascular events; MIMS: *Monthly Index of Medical Specialities*; NICE: National Institute for Health and Care Excellence; NMSC: non-malignant skin cancer; PASI: Psoriasis Area Severity Index; PSSRU: Personal Social Services Research Unit; RCT: randomised controlled trial; TA: technology appraisal: TRAE: treatment-related adverse events. Adapted from Table 41 of the brodalumab NICE submission (TA511).[23]
Note that as the guselkumab appraisal (TA521) followed the NICE fast track appraisal process, the scope and structure of the analysis were not consistent with previous appraisals and so it is not included here

Intervention technology and comparators

Tildrakizumab was included in the analysis as per the anticipated licensed indication for moderate to severe plaque psoriasis (i.e. two doses during the induction period and one dose every 12 weeks during the maintenance period). As described previously, there are two available doses for tildrakizumab (100mg and 200mg). In-line with the SmPC a proportion of patients will be eligible for treatment with the 200mg dose. (See Section B.2.7) As there are no strict criteria for the administration of the 100mg and 200mg doses the two sets of results are presented for the base case analysis – one with 100mg dose only and one 200mg dose only. The impact of separating the overall patient population to one of the two doses is examined via a series of scenario analyses (described in Section B.3.8).

A total of seven comparators identified in the decision problem were included in the analysis: ustekinumab, secukinumab, adalimumab, etanercept, ixekizumab, brodalumab and guselkumab. Each has been recommended by NICE for use within this indication[18-23,25] and will be included in the analysis as per their licensed indication, as summarised in Table 26.

Four additional interventions were also included in the NICE scope: apremilast, DMF, infliximab and BSC. Apremilast and DMF are not deemed to be directly relevant comparators as they are included in a separate part of the NICE pathway for this indication and thus are expected to target a distinct patient population. Infliximab is included in the NICE pathway for very severe psoriasis and is also not a relevant comparator and will not compete directly with tildrakizumab.[16] Furthermore, whilst BSC is included as the final option in all sequences considered as part of the analysis it is not a direct comparator to tildrakizumab as it contains no active therapy.

Table 26: Dosing instructions for all comparators

Treatment	Dosing instruction (including stopping rule)*	Induction period	Annual doses (maintenance only)
Adalimumab	80mg initially and then 1 week after initial dose 40mg every 2 weeks. If no response within 16 weeks then review treatment.	16 weeks	26
Brodalumab	210mg dose per week for 3 weeks followed by 210mg every 2 weeks. If no response after 16 weeks consider discontinuation.	12 to 16 weeks	26
Etanercept (25mg)	25mg twice weekly for 12 weeks. Discontinue if no response after 12 weeks otherwise continue	12 weeks	104

	with 25mg twice weekly.		
Guselkumab	100mg initially followed by 100mg after 4 weeks and then 100mg every 8 weeks as maintenance dose. If no response after 16 weeks consider discontinuation.	16 weeks	6.5
Ixekizumab	160mg initially followed by 80mg after 2 weeks and then 80mg every 2 weeks for a further 5 doses (up to 12 weeks). If no response after 16-20 weeks then consider discontinuation otherwise give a maintenance dose of 80mg every 4 weeks.	12 weeks	13
Secukinumab	300mg every week for 5 doses and then 300mg every month (maintenance). If no response within 16 weeks then review treatment.	16 weeks	12
Ustekinumab	For body-weight up to 100kg give 45mg initially followed by 45mg after 4 weeks and then 45mg every 12 weeks. For body-weight 100kg and above give 90mg initially followed by 90mg after 4 weeks and then 90mg every 12 weeks. For both 45mg and 90mg doses consider discontinuation if no response within 28 weeks.	16 weeks	4.33

*Adapted from information presented in the British National Formulary.[100]

Treatment sequences

NICE and the BAD guidelines recommend that a second or subsequent biologic therapy may be offered if the psoriasis does not respond to a first biologic therapy (see Section B.1.3).[2,26] Discontinuation may occur for the following reasons: inadequate initial response, a subsequent loss of response (i.e. secondary failure), the treatment cannot be tolerated or the treatment subsequently becomes contraindicated.[16] It was advised by clinical experts at a UK Advisory Board[87] that standard practice in the UK now is to attempt three biologic therapies with BSC then administered as the fourth step in the sequence.[87]

The Advisory Board experts also advised that the three most common interventions for moderate to severe plaque psoriasis are currently adalimumab, secukinumab and ustekinumab. They added 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.[87] The latest BAD guidelines recommend that ustekinumab and adalimumab are offered as a first line biological intervention and secukinumab should also be considered.[26]

Based on this information, the tildrakizumab sequence was designated as follows:

Sequence one: Tildrakizumab > ustekinumab > secukinumab > BSC

The results of the NMA (Section B.2.9) indicate that at 12 to 16 weeks adalimumab is less effective than tildrakizumab, whilst tildrakizumab is generally equivalent to ustekinumab and less efficacious than secukinumab. Based on clinical expert advice it is expected that adalimumab would not be administered after tildrakizumab.[87] Therefore, based on the BAD guidelines and clinical expert advice it was determined that the most likely combination post-tildrakizumab would be ustekinumab followed by secukinumab.

Ustekinumab and secukinumab were designated as second and third line options, respectively, for the majority of the comparator sequences to ensure consistent comparisons. However, to fully explore potential permutations, sequences with ustekinumab and secukinumab as first-line options were also modelled. Where ustekinumab was included first line, adalimumab was modelled as the second line option. Where secukinumab was included first line, adalimumab was modelled as the third line option. Ixekizumab, brodalumab and guselkumab are also NICE recommended treatment options for this patient population and have also been included in comparator sequences as shown in Table 27.

Table 27: Summary of comparator sequences included in the analysis

Sequence	First line intervention	Second line intervention	Third line intervention	Fourth line intervention
Two	Adalimumab	Ustekinumab*	Secukinumab	BSC
Three	Ustekinumab*	Adalimumab	Secukinumab	BSC
Four	Secukinumab	Ustekinumab*	Adalimumab	BSC
Five	Etanercept	Ustekinumab*	Secukinumab	BSC
Six	Ixekizumab	Ustekinumab*	Secukinumab	BSC
Seven	Brodalumab	Ustekinumab*	Secukinumab	BSC
Eight	Guselkumab	Ustekinumab*	Secukinumab	BSC

* Ustekinumab was included in the analysis using only studies in line with the licensed weight-based dosing regimen. Sequence one: Tildrakizumab > ustekinumab > secukinumab > BSC. Abbreviation: BSC: best supportive care.

Reporting all possible permutations would be unwieldy given the large number of comparators included in the analysis. To ensure a focused analysis, the sequences were designed based on those most clinically plausible whilst also ensuring that each comparator was included in at least one sequence as a frontline treatment. This is consistent with the two most recent single technology appraisals (STAs) completed in this indication for ixekizumab (TA442)[22] and brodalumab (TA511)[23] (the guselkumab appraisal [TA521] followed the fast-track appraisal (FTA) process and therefore the scope and structure of the analysis was not consistent with previous appraisals).[25]

Additionally, a scenario analysis was run in which 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). (See Scenario 4 Section B.3.8)

B.3.3 Clinical parameters and variables

Treatment effectiveness

The effectiveness of each intervention included in the analysis is based on the relative change in PASI from baseline to the end of the induction phase when each intervention was administered (i.e. PASI response) with a larger change indicating greater response. More specifically, PASI change was categorised into the following three groups: change of ≥50, change of ≥75 and a change of ≥90. This approach is aligned with the original York model developed for the first submissions to NICE in this indication, as well as all other subsequent submissions (excluding guselkumab, which was a FTA that only included a cost comparison). Change in PASI is also the most common method of measuring treatment response in UK clinical practice.[2,26]

The proportion of patients achieving the change in PASI scores defined above (i.e. ≥50, ≥75 and ≥90) was obtained from evidence synthesised via the NMA described in section B.2.9. For each comparator included in the analysis these PASI response rates were estimated by applying relative risk values from the NMA to the response rate for tildrakizumab for each category of PASI score. This equates to the proportion of patients with each treatment reaching the three PASI scores that determine the

model health states (i.e. <50, 50 to 74, 75 to 89, and ≥90) with the values applied in the model summarised in Table 29. The proportion of patients in the <50 health state is the residual of the proportion of patients in the other three health states. These relative risks are summarised in Table 31 and Figure 20. It should also be noted that the response rates for BSC were based on values estimated for placebo patients.

In the economic model, and in line with previous appraisals, all treatments are assumed to have an induction period which is used to establish whether patients have responded to treatment. As described previously, those patients who had a change in PASI of ≥75 at the end of the induction period were defined as responders and thus assumed to remain on treatment into the maintenance period with the response being maintained until discontinuation. Those patients with 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.

It has been assumed that a treatment's position in the sequence does not impact on its effectiveness (i.e. the same PASI response rates are applied regardless of whether the treatment is given first, second or third line). In clinical practice, PASI response may be lower if a treatment is given as a second or third line option, likely as a consequence of the prognosis of patients who have failed to respond to the initial therapy. The evidence for the occurrence of this is variable. An analysis of Danish registry data found that time on treatment, which can be used as a proxy for effectiveness, was significantly shorter for patients who had previously received a biologic therapy whilst other studies (including analyses of registry data) have found no association between drug survival and prior exposure to biologic therapies.[101-104]

The assumptions described above were applied as a consequence of this uncertainty. As the same assumption is applied across all interventions included within the analysis, it is not expected to be a significant driver of the cost-effectiveness results. This approach is aligned with all previous submissions to NICE in this indication.

Table 28: PASI response rates at Week 14 (end of induction period); 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%

Abbreviation: BSC: best supportive care.

Table 29: PASI response rates at Week 14 (end of induction period); 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%

Abbreviation: BSC: best supportive care.

Table 30: Relative risks for each comparator versus tildrakizumab 100mg at 14 weeks

Treatment	Proportion of patients achieving PASI response		
	≥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]

Abbreviation: BSC: best supportive care.

Table 31: Relative risks for each comparator versus tildrakizumab 200mg at 14 weeks

Treatment	Proportion of patients achieving PASI response		
	≥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]

Abbreviation: BSC: best supportive care.

Discontinuation

For patients who move into the maintenance period for a specific intervention there is an ongoing risk of discontinuation. Discontinuation may occur due to a subsequent loss of efficacy (i.e. a worsening of PASI score) or the development of a contraindication. For all previous NICE appraisals in this indication an annual discontinuation rate of approximately 20% has been applied consistently across all interventions.

The recent STA for brodalumab used a value of 18.7%, based on an analysis of data from the British Association of Dermatologists Biologic Interventions Register (BADBIR), an approach that appeared to have been accepted by the Evidence Review Group (ERG) or committee.[23] Therefore, the same value was adopted for this analysis. To be applicable for the adopted model structure the annual values were converted to a 14 week probability of discontinuation, which equates to a value of 4.67%. This conversion was based on the following equation:

$$x = e^{\text{Ln}\,(1-y)\,/\,(52/12)}$$

Where: x = discontinuation rate per model cycle

y = annual discontinuation rate

It is possible that discontinuation rates may vary depending on the chosen intervention. However, there were insufficient data for the inclusion of treatment-specific discontinuation rates. This is because, for a number of treatments in the

analysis, including tildrakizumab, the only available data sources were RCTs and given the strict protocols for these studies they will not be reflective of discontinuation in clinical practice.

Nevertheless, data are available from registry studies, which could be more reflective of discontinuation rates observed in routine clinical practice, for the more established treatments in this indication (i.e. etanercept, adalimumab, ustekinumab and secukinumab). Therefore, the impact of the adoption of these data was explored via a scenario analysis with full details provided in Section B.3.8.

Mortality

Mortality for the general population was included in the model to capture the number of deaths, based on life tables for England and Wales.[105] Age and gender stratified rates were used, such that the rates changed as the cohort included in the model aged. The starting age in the model was 46, based on the mean age of patients in the two pivotal tildrakizumab RCTs. The prevalence of psoriasis is balanced between genders so the mortality rates were based on a 50:50 split of males and females.[106]

Mortality data for the general population in England and Wales is reported as annual rates so these were converted to 14 week probabilities using the same equation outlined above for the discontinuation rate conversion.

Previous research indicates that mortality may be higher in the severe plaque psoriasis population, perhaps due to the presence of comorbid diseases, as shown by a hazard ratio (HR) of 1.42 (95% CI: 1.25 to 1.62) for severe psoriasis patients versus matched controls.[107] This study also reported no statistically significant difference in the rate of death for patients with mild psoriasis compared with matched controls from the general population (HR = 1.10; 95% CI: 0.97 to 1.02).

The impact of moderate psoriasis on the risk of mortality is unclear as no data on this subgroup were reported by Gelfand et al.[107] Therefore, given the relevant population of the analysis (i.e. patients with moderate to severe plaque psoriasis), no increased risk of mortality was modelled in the base case. However, this was explored further as a scenario analysis, which is described in more detail in Section B.3.8.

Overall, the choice of treatment was assumed to have no impact on the mortality rate within the model. This approach was confirmed as valid by the clinical experts at the UK Advisory Board[87] and is also aligned with all previous submissions in this indication.

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

HRQoL data were collected using the DLQI instrument within the tildrakizumab reSURFACE studies. In both reSURFACE 1 and reSURFACE 2, tildrakizumab 200mg was associated with statistically significant improvement in HRQoL. At Week 12, 44.1% and 47.4% of patients treated with tildrakizumab 200mg achieved a DLQI score of 0 or 1 in the reSURFACE 1 and 2 studies, respectively. Improvements were maintained over time; 68.4% of patients receiving tildrakizumab 200mg who were PASI 75 responders at Week 28 had a DLQI score of 0 or 1 at the end of Part 3 (Week 64) in the reSURFACE 1 study. The corresponding figure in the reSURFACE 2 study was 72.4% at Week 52 (Section B.2.6.6).

The DLQI is a disease-specific instrument making it inconsistent with the NICE reference case. Therefore, it was determined that the direct application of this data would not be appropriate for the cost-effectiveness analysis.

As described in Section B.2.6, EQ-5D-3L data were also collected as an exploratory endpoint in the reSURFACE1 study. Index utility estimates were calculated based on the EQ-5D data collected in the reSURFACE study using the European valuation set. Pooled across all three interventions (i.e. 100mg tildrakizumab, 200mg tildrakizumab and placebo) the baseline utility was 0.61 (95% CI: 0.58 to 0.63). At week 12 there was an improvement in utility with a mean value of 0.81 recorded.

Mapping

In previous submissions to NICE in this indication (TA103 and TA180) mapping of DLQI to EQ-5D was undertaken in order to meet the requirements of the NICE reference case[18,20] and the methods for this mapping process are available and have been previously validated. However, there is already a large pool of available utility

data available in this indication, which is described further below. Given the availability of such data it was deemed unnecessary to replicate the DLQI mapping with the tildrakizumab. Changes to the base case utility values were also explored during sensitivity and scenario analyses to examine the importance of the data that were applied.

Health-related quality-of-life studies

A SLR for HRQoL data was undertaken with full methods and results described in Appendix H. A total of 39 full text documents and 12 conference abstracts were eligible following the review. These records reported data from RCTs, a pooled analysis of two RCTs, five cross-sectional studies or surveys, two prospective observational studies, one single-arm study, one cohort study, three retrospective reviews of registry data and twelve economic evaluations based on decision models (with utility data generally based on clinical trials).

Given the structure of the model, there is a requirement to include utility data that quantifies patient HRQoL dependent on the pre-specified PASI response model health states (i.e. <50, 50 to 74, 75 to 90 and >90). Also, the NICE reference case states that utility data should be based on the EQ-5D survey instrument.[34] Finally, previous submissions to NICE in this indication have focused on patients with a DLQI score >10, an approach that was deemed acceptable by the ERG and committee during each appraisal. Therefore, Table 32 presents the identified EQ-5D utility data that also fit the health states of the model and is based on patients with a DLQI score >10. The majority of the data presented were identified in previous NICE appraisals and excludes sources that repeat data presented elsewhere.

Table 32: Summary of EQ-5D utility values by health state, as identified in SLR, including previous technology appraisals

Study Reference	Baseline	Change in utility				Comments
		PASI <50	***PASI 50 to 74***	***PASI 75 to 90***	***PASI ≥90***	
Etanercept and efalizumab (TA103)[18]	Not reported	0.12 (SE 0.03)	0.29 (SE 0.06)	0.38 (SE 0.08)	0.41 (SE 0.09)	4th quartile DLQI (assumed equivalent to DLQI >10)
Adalimumab (TA146)[19]	Not reported	0.063 (SE 0.025)	0.178 (SE 0.023)	0.178 (SE 0.023)	0.308 (SE 0.027)	

Ustekinumab (TA180)[20]	Not reported	0.04	0.17	0.22	0.25	
Secukinumab (TA350)[21]	0.642	0.11	0.19	0.23	0.26	
Ixekizumab (TA442)[22]	Not reported	0.0012 (SE 0.006)	0.100 (SE 0.010)	0.131 (SE 0.008)	0.144 (SE 0.007)	PASI 100: 0.153
Brodalumab (TA511)[23]	0.521	0.016	0.190	0.295	0.355	PASI 100: 0.368
Pickard *et al.* 2017[108]	0.660	0.029 (SE 0.010)	0.125 (SE 0.016)	0.166 (SE 0.012)	0.184 (SE 0.010)	

Abbreviations: DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area Severity Index; SE: standard error; SLR: systematic literature review; TA; technology appraisal.

Health-related quality-of-life data used in the cost-effectiveness analysis

Health state utilities were applied in the model based on the EQ-5D data recorded at week 12 of the reSURFACE trial. Given the patient population included in the analysis, these data were taken from all patients with a DLQI >10 at study baseline, which equates to a 482 patients from a total cohort of 772. The data from these patients were pooled across all three treatment arms and stratified by PASI response in order to estimate values there were applicable to the model health states, with these values summarised in Table 33. The values shown are largely consistent with those reported in Table 32. A scenario analysis was also undertaken in which data from previous submissions were adopted for utility to examine the overall impact on the results.

The impact of psoriasis on patient HRQoL is assumed to be constant (i.e. the utility gains with each level of PASI response remain unchanged throughout the model time horizon). However, as a lifetime horizon has been adopted a general decline in HRQoL with age has been modelled. To model this decline, first for each of the PASI response categories (i.e. <50, 50 to 74, 75 to 90 and >90) the percentage change in utility from the population norm value was estimated based on age-specific population norm utility and the utility change values reported in Table 33. These data are presented in Table 34. An age-specific population norm utility value of 0.871 was applied. This is the utility of the general population when aged 46, which was the starting age of the cohort included in the model, based on data reported by Kind et al.[109] The utility by PASI response was then estimated for all ages >46 by applying the percentage change values estimated previously to the population norm value for each age, again based on data reported by Kind et al.[109] The correct age-specific

utility values were then applied in the model, dependent on the age of the cohort within each cycle of the model.

Utility values were dependent only on the health state (by PASI response) plus the number of patients residing within each state. They were therefore independent from the administered treatment.

Table 33: Summary of utility values for cost-effectiveness analysis, DLQI >10

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

Abbreviations: PASI: Psoriasis Area Severity Index

Table 34: Summary of percentage change in utility values 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]

Abbreviations: PASI: Psoriasis Area Severity Index

Adverse reactions

Adverse reactions, including the impact on patient HRQoL, were not explicitly modelled as part of the analysis. The rate of adverse reactions in the tildrakizumab studies was low (see section B.2.10), consistent with experience for other biologic psoriasis treatments. Furthermore, given the low incidence of adverse events for tildrakizumab and included comparators it is expected their inclusion would have no meaningful impact on the results of the analysis.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

A SLR was undertaken to search for relevant cost and healthcare resource data with the full methods and results described in Appendix I.

In line with the NICE reference case[34] only direct medical costs have been captured as part of the analysis and unit costs have been sourced from recognised national sources, where possible (namely: NHS Reference Costs 2016/17[110], the British National Formulary [BNF][100] and the Personal Social Services Research Unit [PSSRU][111]). Where it was only possible to identify unit costs based on pre-2016 prices, the costs were inflated to 2016/17 prices using the hospital and community health services inflation index that is published by PSSRU.[112]

Intervention and comparators' costs and resource use

Drug acquisition costs

For the unit cost of tildrakizumab, a PAS has been submitted to the Patient Access Scheme and Liaison Unit (PASLU) and the Department of Health in the form of a simple discount of [redacted]. Taking this PAS into consideration, the price per pack applied in the model is [redacted]

Table 35 shows the unit costs of all comparators based on list prices published by the BNF.[100] Secukinumab, ixekizumab, brodalumab and guselkumab have all been recommended by NICE in this indication under the condition that they are provided at an agreed PAS discount price. The PAS discounts are confidential and, therefore, could not be included in the analysis. Ustekinumab was originally approved based on an agreed PAS, which was later withdrawn as the company now provides the 90mg dose at the same cost as the 45mg vial; this price is included in the analysis. Biosimilar etanercept is also available. This analysis assumes that biosimilar and branded etanercept have equivalent efficacy and therefore, the cheapest formulation (i.e. the biosimilar) would always be selected by the NHS.

The total cost per treatment for the induction and maintenance period were estimated by multiplying the dose required for that period by the unit cost (with adjustments made to account for the total dose per unit). As the administration procedure with each treatment did not always align exactly with the 14-week cycle length in the model, adjustments were also made to the trial and maintenance doses to ensure the correct dose was given for a 14-week period. For example, during the

maintenance period tildrakizumab is administered every 12 weeks. Therefore, for each 14-week maintenance cycle in the model it was assumed 1.17 doses were given (14/12 = 1.17), which equates to a dose of 233mg per cycle.

Table 35: Overview of treatment costs

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	£3,983
Brodalumab	£1,280	2	210	1680	1470	£5,120	£4,480
Guselkumab	£2,250	1	100	300	188	£6,750	£4,230

*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]

Administration costs

All treatments included in the analysis are given via a self-administered sc injection. There may be a small cost associated with this self-administration, such as training by a nurse upon treatment initiation. However, it is expected that training would be administered just once to all patients at initiation of the first treatment in the sequence, regardless of which treatment is selected first, and would not be required again. Therefore, the choice of treatment has no impact on the costs so this has not been captured within the analysis.

Monitoring costs

For moderate to severe plaque psoriasis patients, monitoring costs include outpatient visits and a small number of diagnostic tests. The type and frequency of visits / tests included in the model was based on cost-effectiveness analysis undertaken as part of the NICE clinical guideline for psoriasis (CG153).[5] These values also align with the latest guidance from BAD on recommended investigations for psoriasis patients.[26] The NICE clinical guideline included three biologic therapies

in their cost-effectiveness model (adalimumab, etanercept and ustekinumab) with the same resource use values applied across all treatments. Therefore, based on the approach adopted in that model, the same resource use values have been applied to all biologic treatments included in this analysis.

Separate resource use values were applied to the induction and maintenance periods in the model, in line with the approach adopted by NICE for CG153.[2] Unit costs for each resource were obtained from NHS Reference Costs 2016/17.[110] The total cost associated with each resource is summarised in Table 36.

Best supportive care costs

As with monitoring costs, the cost of BSC was based on values adopted in the cost-effectiveness model developed for the NICE clinical guideline (CG153).[5] Within this model, the following resources were captured: drug therapy, phototherapy, day centre care and inpatient care (separated into 'high need' and 'very high need'). The costs reported in the clinical guideline were inflated from 2012 to 2017 prices using the inflation indices described previously. These costs are summarised in Table 37.

The clinical experts at the UK Advisory Board noted that there is a degree of uncertainty regarding the total cost of BSC due to a lack of recent studies to quantify the true cost in clinical practice.[87] The two most recent NICE submissions in this indication (i.e. ixekizumab [TA442][22] and brodalumab [TA511][23]) used data reported by Fonia and colleagues.[113] These data were generated from 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. However, the clinical experts consulted advised that this study is now out of date given the time that has elapsed since its completion,[87] which is why it has not been adopted for the base case analysis. Nevertheless, these data were examined in a scenario analysis and an extensive range of values were applied for this parameter during sensitivity analysis.

Health-state unit costs and resource use

No health state-specific costs were included in the model (i.e. by PASI response).

Adverse reaction unit costs and resource use

As described previously, adverse reactions have not been included in the analysis so no costing inputs relating to these events were modelled.

Miscellaneous unit costs and resource use

No other health care resources were included in the analysis.

Table 36: Background resource use in trial period (one-cycle)

Resource	Unit cost (£)	Service / Currency code	Resource use		Total cost		References
			Induction period	Maintenance period	Induction period	Maintenance period	
Outpatient visits	£103	Outpatient attendance (330)	2	1	£206.09	£103.05	Unit cost: NHS reference costs[110] Resource use: NICE clinical guideline CG153[5]
Liver Function Test	£1.13	DAPS04	2	1	£2.25	£1.13	
Full blood count	£1.13	DAPS04	2	1	£2.25	£1.13	
Urea and electrolytes	£1.13	DAPS04	2	1	£2.25	£1.13	

Abbreviations: CG: clinical guideline; NHS: National Health Service.

Table 37: Best supportive care cost and resource use

Items	Resource use	Average annual cost	Cost per cycle	Reference
Drugs				NICE clinical guideline CG153[5] Costs inflated from 2011/12 to 2015/16 using HCHS inflation indices[112]
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**	

Abbreviations: CG: Clinical Guideline; HCHS: Hospital and Community Health Service; N/A: not available; NICE: National Institute for Health and Care Excellence; PSSRU: Personal Social Services Research Unit; UVB: Ultraviolet B.

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

The base case model parameters are summarised in Table 38.

Table 38: Summary of variables applied in the economic model

	Variable	Value	Measurement of uncertainty and distribution: CI	Reference to section in submission
Model settings	Discount rate (costs)	3.5%	N/A	B.3.2
	Discount rate (benefits)	3.5%	N/A	
Patient characteristics	Age	46 years	N/A	B.3.2
	Male	50.0%	N/A	
PASI scores: Tildrakizumab (100mg)	PASI 50	[redacted]	N/A	B.3.3
	PASI 75	66.70%	N/A	
	PASI 90	41.53%	N/A	
Relative risk: Adalimumab (100mg)	PASI 50	[redacted]	[redacted]	
	PASI 75			
	PASI 90			
Relative risk: Brodalumab (100mg)	PASI 50			
	PASI 75			
	PASI 90			
Relative risk: Etanercept (100mg)	PASI 50			
	PASI 75			
	PASI 90			
Relative risk: Guselkumab (100mg)	PASI 50			
	PASI 75			
	PASI 90			
Relative risk: Ixekizumab (100mg)	PASI 50			
	PASI 75			
	PASI 90			
Relative risk: Secukinumab (100mg)	PASI 50			
	PASI 75			
	PASI 90			
Relative risk: Ustekinumab (100mg)	PASI 50			
	PASI 75			
	PASI 90			
Relative risk: BSC (100mg)	PASI 50			
	PASI 75			
	PASI 90			
PASI scores: Tildrakizumab (200mg)	PASI 50	[redacted]	N/A	B.3.3
	PASI 75	69.55%	N/A	
	PASI 90	44.67%	N/A	
Relative risk: Adalimumab (200mg)	PASI 50	[redacted]	[redacted]	
	PASI 75			
	PASI 90			
Relative risk: Brodalumab (200mg)	PASI 50			
	PASI 75			
	PASI 90			
Relative risk: Etanercept (200mg)	PASI 50			
	PASI 75			
	PASI 90			

Relative risk: Guselkumab (200mg)	PASI 50	[redacted]	[redacted]	
	PASI 75			
	PASI 90			
Relative risk: Ixekizumab (100mg)	PASI 50			
	PASI 75			
	PASI 90			
Relative risk: Secukinumab (200mg)	PASI 50			
	PASI 75			
	PASI 90			
Relative risk: Ustekinumab (200mg)	PASI 50			
	PASI 75			
	PASI 90			
Relative risk: BSC (200mg)	PASI 50			
	PASI 75			
	PASI 90			
Annual rate of treatment discontinuation	All therapies (apart from BSC)	18.7%	N/A	B.3.3
Baseline utility		0.61	N/A	B.3.4
Utility by PASI response	PASI <50	0.67	SE = 0.025	
	PASI ≥50-<75	0.83	SE = 0.020	
	PASI ≥75-<90	0.85	SE = 0.020	
	≥90	0.89	SE = 0.012	
Drug unit costs	Tildrakizumab 100mg	[redacted]	N/A	B.3.5
	Tildrakizumab 200mg		N/A	
	Etanercept 25mg	£321.75	N/A	
	Adalimumab 40mg	£704.28	N/A	
	Ustekinumab 45mg	£2,147.00	N/A	
	Secukinumab 150mg	£1,218.87	N/A	
	Ixekizumab 80mg	£1,125.00	N/A	
	Brodalumab 210mg	£1,280.00	N/A	
	Guselkumab 100mg	£2,250.00	N/A	
Background resource unit costs	Outpatient visit	£103.05	N/A	
	Liver function test	£1.13	N/A	
	Full blood count	£1.13	N/A	
	Urea and electrolytes	£1.13	N/A	
	Inpatient stay	£2,622.06	N/A	
	A&E visits	£100.00	N/A	
	Day ward admissions	£239.68	N/A	
	Phototherapy	£86.95	N/A	
	PIIINP	£26.59	N/A	
	Glomerular filtration rate	£186.81	N/A	
	Liver biopsy	£690.50	N/A	
Background resource use: trial period (one cycle)	Outpatient visit	2	N/A	
	Liver function test	2	N/A	
	Full blood count	2	N/A	
	Urea and electrolytes	2	N/A	
Background resource use: maintenance period (one cycle)	Outpatient visit	1	N/A	
	Liver function test	1	N/A	
	Full blood count	1	N/A	
	Urea and electrolytes	1	N/A	
	Inpatient stay	0.42	N/A	
	Day ward admissions	0.31	N/A	
BSC cost per cycle	Methotrexate	£51.41	N/A	
	Ciclosporin	£302.16	N/A	
	No drug (outpatient visits)	£8.49	N/A	
	Day care centre visits	£513.07	N/A	

	Narrow-band UVB sessions	£85.21	N/A	
	Inpatient care: high need admissions	£1,363.88	N/A	
	Inpatient care: very high need admissions	£763.44	N/A	

Abbreviations: A&E: accident and emergency; BSC: best supportive care; CI: confidence interval; N/A: not available; PASI: Psoriasis Area and Severity Index; PIIINP: N-Terminal Propeptide of Type III Collagen; SE: standard error; UVB: ultraviolet B.

Assumptions

The assumptions adopted in the analysis are summarised and justified in Table 39.

Table 39: Summary of assumptions in the analysis

Assumption	Justification	Consistent with previous appraisals?
The effectiveness of each treatment, in terms of PASI response at the end of the induction period, was assumed to remain sustained until patients discontinued from treatment during the maintenance period.	Evidence for biologic therapies[30,101] indicate that the biggest reason for discontinuation is a poor initial response but for those who respond adequately and move onto the maintenance period treatment efficacy is well sustained. There is also an absence of long term data on PASI response for all comparators included in the analysis.	Yes
The effectiveness of each treatment was assumed to be unaffected by the position of the treatment in the overall sequence.	No evidence was available to quantify position-specific PASI responses for all treatments	Yes
The rate of discontinuation was assumed to be constant throughout the model time horizon with the same rate applied to all treatments.	Due to a paucity of non-RCT data it was not possible to include treatment-specific discontinuation rates for all interventions included in the analysis.	Yes
A lifetime horizon was adopted.	Lifetime used to capture all costs and QALYs associated with each treatment sequence.	Partially (see Table 25)
No adverse events were included in the analysis.	Biologic therapies are well tolerated in this indication meaning the rate of adverse events is low. Therefore, the exclusion of these events is not expected to alter the results of the analysis.	Partially (see Table 25)
Mortality of the population included in the analysis is not greater than the general population.	There is no evidence of increased mortality for moderate to severe patients (evidence for severe only).	Partially (see Table 25)

Abbreviations: PASI: Psoriasis Area and Severity Index; QALY: quality-adjusted life year; RCT: randomised controlled trial.

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

A summary of base case cost-effectiveness results for tildrakizumab 100mg and 200mg are presented in Table 40 and Table 41 respectively. Incremental cost-effectiveness ratios (ICERs) are presented for a fully incremental analysis. Also, for a pairwise analysis the incremental net monetary benefit (INMB) of the tildrakizumab sequence versus each comparator sequence is presented based on a cost-effectiveness threshold of £20,000 per QALY.

Throughout this section results are displayed in the tables in order of increasing incremental costs.

B.3.7.1 Tildrakizumab 100mg

In the fully incremental analysis, tildrakizumab (sequence 1), which is associated with the lowest total cost, was the reference comparator. Secukinumab (sequence 4), ixekizumab (sequence 6) and brodalumab (sequence 7) were both [redacted] costly and [redacted] effective than tildrakizumab (sequence 1), with ICERs of £3,492,492, £155,597 and £200,800 per QALY, respectively. As secukinumab was associated with an ICER higher than that of two more effective interventions (ixekizumab and brodalumab) it was extendedly dominated by those sequences. The other comparator sequences were dominated.

The pairwise analysis also indicates that the tildrakizumab sequence generated a positive NMB versus each individual comparator sequence.

Based on a cost-effectiveness threshold of £20,000 to £30,000 per QALY gained, the tildrakizumab sequence (sequence 1) was the most cost-effective choice.

Table 40: Base case 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

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.

B.3.7.2 Tildrakizumab 200mg

In the fully incremental analysis, tildrakizumab (sequence 1), which was associated with the lowest total cost, was the reference comparator. Ixekizumab (sequence 6) was [redacted] costly and [redacted] effective than tildrakizumab (sequence 1), with an ICER of £182,232 per QALY. The other comparator sequences were all dominated.

The pairwise analysis also indicates that the tildrakizumab sequence generated a positive NMB versus each individual comparator sequence.

Based on a cost-effectiveness threshold of £20,000 to £30,000 per QALY gained, the tildrakizumab sequence (sequence 1) was the most cost-effective choice.

Table 41: Base case results, tildrakizumab 200mg

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	£236,551	[redacted]	[redacted]	[redacted]	Dominated	£4,983
2	ADA	UST	SEC	BSC	£237,054	[redacted]	[redacted]	[redacted]	Dominated	£1,907
3	UST	ADA	SEC	BSC	£237,817	[redacted]	[redacted]	[redacted]	Dominated	£2,657
4	SEC	UST	ADA	BSC	£245,960	[redacted]	[redacted]	[redacted]	Dominated	£10,633
6	IXE	UST	SEC	BSC	£264,968	[redacted]	[redacted]	[redacted]	£182,232	£26,020
8	GUS	UST	SEC	BSC	£265,109	[redacted]	[redacted]	[redacted]	Dominated	£26,927
7	BRO	UST	SEC	BSC	£267,105	[redacted]	[redacted]	[redacted]	Dominated	£28,158

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.

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was undertaken with 1,000 model simulations. A full list of all parameters included in the PSA is presented in Table 42. Probability distributions were based on sampling error estimates from data sources, such as confidence intervals. In the absence of data on the variability around the sampling distribution of mean values, the standard error was assumed to be equal to 25% of the mean.

Log normal distributions were used for treatment effects such as odds ratios, and gamma distributions were used for utility changes and costs applied in the model.

A summary of the probabilistic results for tildrakizumab 100mg and 200mg are presented in Table 43 and Table 44 respectively.

B.3.8.1 Tildrakizumab 100mg

Overall, the results of the PSA are similar to the base case analysis with the tildrakizumab sequence being the most cost-effective choice at a threshold of £20,000 to £30,000.

Tildrakizumab (sequence 1) was the treatment with the lowest costs. When compared pairwise to each treatment sequence, tildrakizumab (sequence 1) was associated with ICERs ranging from £152,838 versus ixekizumab (sequence 6) to £2,107,395 versus secukinumab (sequence 4). Brodalumab (sequence 7) was the most costly sequence, generating [redacted] more QALYs than the tildrakizumab sequence with an ICER of £163,483. Tildrakizumab (sequence 1) dominated etanercept (sequence 5), adalimumab (sequence 2) and ustekinumab (sequence 3).

A graphical depiction of the simulations is presented in Figure 24.

Table 42: Summary of parameters included in the probabilistic sensitivity analysis

Parameter	Base case	Standard error	Distribution
Treatment effectiveness – PASI 50 (relative risk); 100mg			
Adalimumab	[redacted]	0.036	Lognormal
Brodalumab	[redacted]	0.029	
Etanercept	[redacted]	0.045	
Guselkumab	[redacted]	0.033	
Ixekizumab	[redacted]	0.027	
Secukinumab	[redacted]	0.030	
Ustekinumab	[redacted]	0.035	
BSC	[redacted]	0.054	
Treatment effectiveness – PASI 75 (relative risk); 100mg			
Adalimumab	[redacted]	0.070	Lognormal
Brodalumab	[redacted]	0.056	
Etanercept	[redacted]	0.081	
Guselkumab	[redacted]	0.063	
Ixekizumab	[redacted]	0.054	
Secukinumab	[redacted]	0.058	
Ustekinumab	[redacted]	0.069	
BSC	[redacted]	0.057	
Treatment effectiveness – PASI 90 (relative risk); 100mg			
Adalimumab	[redacted]	0.116	Lognormal
Brodalumab	[redacted]	0.099	
Etanercept	[redacted]	0.134	
Guselkumab	[redacted]	0.110	
Ixekizumab	[redacted]	0.096	
Secukinumab	[redacted]	0.102	
Ustekinumab	[redacted]	0.115	
BSC	[redacted]	0.177	
Treatment effectiveness – PASI 50 (relative risk); 200mg			
Adalimumab	[redacted]	0.034	Lognormal
Brodalumab	[redacted]	0.025	
Etanercept	[redacted]	0.047	
Guselkumab	[redacted]	0.028	
Ixekizumab	[redacted]	0.025	
Secukinumab	[redacted]	0.026	
Ustekinumab	[redacted]	0.033	
BSC	[redacted]	0.041	
Treatment effectiveness – PASI 75 (relative risk); 200mg			
Adalimumab	[redacted]	0.067	Lognormal
Brodalumab	[redacted]	0.050	
Etanercept	[redacted]	0.082	
Guselkumab	[redacted]	0.059	
Ixekizumab	[redacted]	0.050	

Secukinumab	[redacted]	0.053	
Ustekinumab	[redacted]	0.064	
BSC	[redacted]	0.064	
Treatment effectiveness – PASI 90 (relative risk); 200mg			
Adalimumab	[redacted]	0.111	Lognormal
Brodalumab	[redacted]	0.094	
Etanercept	[redacted]	0.128	
Guselkumab	[redacted]	0.104	
Ixekizumab	[redacted]	0.092	
Secukinumab	[redacted]	0.098	
Ustekinumab	[redacted]	0.111	
BSC	[redacted]	0.177	
Utility by PASI response			
<50	0.67	0.025	Gamma
≥50 to <75	0.83	0.020	
≥75 to <90	0.85	0.020	
≥90	0.89	0.013	
Background costs (per cycle)			
Induction period (all treatments)	£212.85	£53.21	Gamma
Maintenance period (all treatments)	£106.43	£26.61	
Best supportive care costs (per cycle)			
Total cost	**£3,087.66**	**£771.92**	**Gamma**

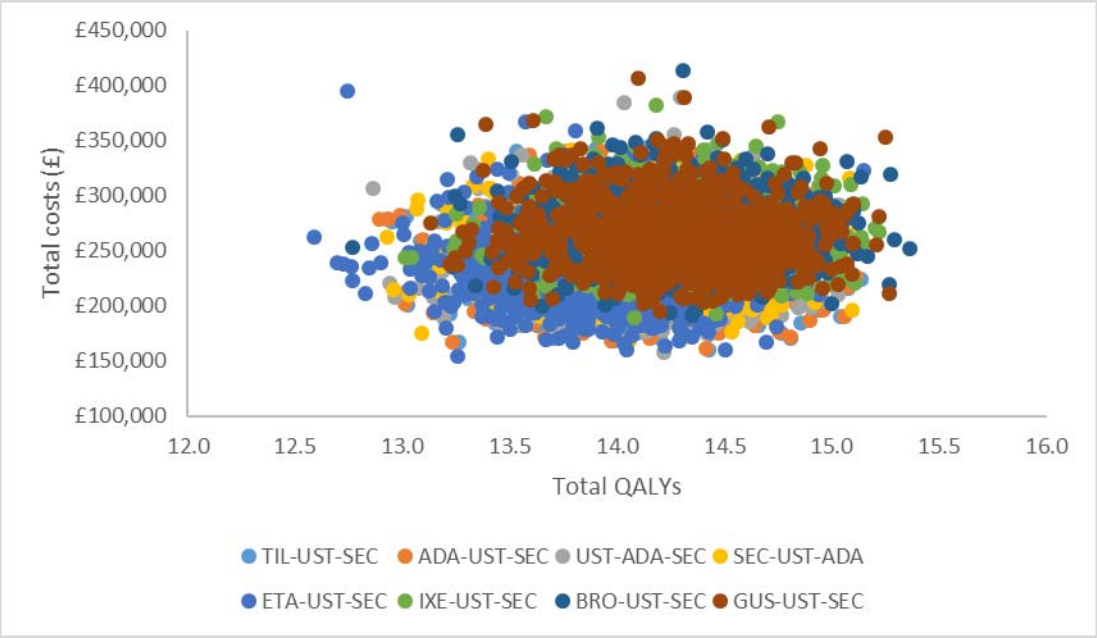
Abbreviations: BSC: best supportive care; PASI: Psoriasis Area and Severity Index.

Table 43: Results of probabilistic sensitivity analysis, tildrakizumab 100mg

Sequence (first treatment only shown)	Total QALYs		Total costs		Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator)
	Mean	95% CrI	Mean	95% CrI		
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

Abbreviations: CrI: credible interval: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; N/A: not available; QALY: quality-adjusted life year.

Figure 24: PSA scatterplot on cost effectiveness plane



Abbreviations: ADA: adalimumab; BRO: brodalumab; ETA: etanercept; GUS: guselkumab; IXE: ixekizumab; PSA: probabilistic sensitivity analysis; SEC: secukinumab; TIL: tildrakizumab; UST: ustekinumab.

B.3.8.2 Tildrakizumab 200mg

Overall, the results of the PSA were similar to the base case analysis with the tildrakizumab sequence being the most cost-effective choice at a threshold of £20,000 to £30,000.

Tildrakizumab (sequence 1) was the treatment with the lowest costs. When compared pairwise to each treatment sequence, tildrakizumab (sequence 1) was associated with ICERs ranging from £182,935 versus ixekizumab (sequence 6) to £235,430 versus guselkumab (sequence 8). Brodalumab (sequence 7) was the most costly sequence, generating [redacted] QALYs than the tildrakizumab sequence with an ICER of £192,961. Tildrakizumab (sequence 1) dominated etanercept (sequence 5), adalimumab (sequence 2), ustekinumab (sequence 3) and secukinumab (sequence 4).

A graphical depiction of the simulations is presented in Figure 25.

Table 44: Results of probabilistic sensitivity analysis, tildrakizumab 200mg

Sequence (first treatment only shown)	Total QALYs		Total costs		Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator)
	Mean	95% CrI	Mean	95% CrI		
1: Tildrakizumab	[redacted]	[redacted]	[redacted]	[redacted]	-	N/A
5: Etanercept	[redacted]	[redacted]	£236,498	£188,359 to £290,338	Dominated	£4,980
2: Adalimumab	[redacted]	[redacted]	£237,093	£191,674 to £288,774	Dominated	£1,913
3: Ustekinumab	[redacted]	[redacted]	£238,369	£190,188 to £294,059	Dominated	£2,605
4: Secukinumab	[redacted]	[redacted]	£248,380	£199,139 to £307,213	Dominated	£10,625
6: Ixekizumab	[redacted]	[redacted]	£263,660	£219,079 to £314,173	£182,935	£26,066
8: Guselkumab	[redacted]	[redacted]	£264,591	£221,279 to £318,553	Dominated	£26,950
7: Brodalumab	[redacted]	[redacted]	£265,236	£219,362 to £317,208	Dominated	£28,251

Abbreviations: CrI: credible interval: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; N/A: not available; QALY: quality-adjusted life year.

Figure 25: PSA scatterplot on cost effectiveness plane

Abbreviations: ADA: adalimumab; BRO: brodalumab; ETA: etanercept; GUS: guselkumab; IXE: ixekizumab; PSA: probabilistic sensitivity analysis; SEC: secukinumab; TIL: tildrakizumab; UST: ustekinumab.

Deterministic sensitivity analysis

One-way sensitivity analyses (OWSA) were undertaken to assess the impact of key variables on the model outcomes (Table 45). 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.

Table 45: Inputs for one-way sensitivity analysis

Parameter	Mean	Lower bound	Upper bound
Unit cost of tildrakizumab	[redacted]	[redacted]	[redacted]
Cost of BSC per cycle	£3,088	£1,544	£4,632
Baseline utility	[redacted]	[redacted]	[redacted]
Utility - PASI score <50	[redacted]	[redacted]	[redacted]
Utility - PASI score ≥50 to <75	[redacted]	[redacted]	[redacted]
Utility - PASI score ≥75 to <90	[redacted]	[redacted]	[redacted]
Utility - PASI score ≥90	[redacted]	[redacted]	[redacted]
Treatment discontinuation – cycle probability	[redacted]	[redacted]	[redacted]
Tildrakizumab 100mg			
Tildrakizumab PASI score 90	41.53%	34%	49%
Tildrakizumab PASI score 75	66.70%	60%	73%
Tildrakizumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk - etanercept PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk - etanercept PASI score 75	[redacted]	[redacted]	[redacted]

Relative risk - etanercept PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk - adalimumab PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk - adalimumab PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk - adalimumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk - ustekinumab PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk - ustekinumab PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk - ustekinumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk - secukinumab PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk - secukinumab PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk - secukinumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk – ixekizumab PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk – ixekizumab PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk – ixekizumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk – brodalumab PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk – brodalumab PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk – brodalumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk – guselkumab PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk – guselkumab PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk – guselkumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk - BSC PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk - BSC PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk - BSC PASI score 50	[redacted]	[redacted]	[redacted]
Tildrakizumab 200mg			
Tildrakizumab PASI score 90	44.67%	37%	52%
Tildrakizumab PASI score 75	69.55%	63%	76%
Tildrakizumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk - etanercept PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk - etanercept PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk - etanercept PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk - adalimumab PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk - adalimumab PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk - adalimumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk - ustekinumab PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk - ustekinumab PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk - ustekinumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk - secukinumab PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk - secukinumab PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk - secukinumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk – ixekizumab PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk – ixekizumab PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk – ixekizumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk – brodalumab PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk – brodalumab PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk – brodalumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk – guselkumab PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk – guselkumab PASI score 75	[redacted]	[redacted]	[redacted]

Relative risk – guselkumab PASI score 50	[redacted]	[redacted]	[redacted]
Relative risk - BSC PASI score 90	[redacted]	[redacted]	[redacted]
Relative risk - BSC PASI score 75	[redacted]	[redacted]	[redacted]
Relative risk - BSC PASI score 50	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; PASI: Psoriasis Area and Severity Index.

B.3.8.3 Tildrakizumab 100mg

The tornado diagrams in Figure 26 to Figure 32 show the variation in base-case NMB from OWSA (tildrakizumab 100mg versus comparator). The main drivers of NMB across comparisons were the discontinuation rate, unit cost of tildrakizumab and maintenance dose of tildrakizumab.

Figure 26: OWSA results (tildrakizumab 100mg versus etanercept)

Figure 27: OWSA results (tildrakizumab 100mg versus adalimumab)

Figure 28: OWSA results (tildrakizumab 100mg versus ustekinumab)

Figure 29: OWSA results (tildrakizumab 100mg versus secukinumab)

Figure 30: OWSA results (tildrakizumab 100mg versus ixekizumab)

Figure 31: OWSA results (tildrakizumab 100mg versus brodalumab)

Figure 32: OWSA results (tildrakizumab 100mg versus guselkumab)

B.3.8.4 Tildrakizumab 200mg

The tornado diagrams in Figure 33 to Figure 39 show the variation in base-case NMB from OWSA (tildrakizumab 200mg versus comparator). The main drivers of NMB across comparisons were the discontinuation rate, unit cost of tildrakizumab and maintenance dose of tildrakizumab.

Figure 33: OWSA results (tildrakizumab 200mg versus etanercept)

Figure 34: OWSA results (tildrakizumab 200mg versus adalimumab)

Figure 35: OWSA results (tildrakizumab 200mg versus ustekinumab)

Figure 36: OWSA results (tildrakizumab 200mg versus secukinumab)

Figure 37: OWSA results (tildrakizumab 200mg versus ixekizumab)

Figure 38: OWSA results (tildrakizumab 200mg versus brodalumab)

Figure 39: OWSA results (tildrakizumab 200mg versus guselkumab)

Scenario analysis

Structural uncertainty was explored by generating results using alternative assumptions for key input parameters. The results of the base case, probabilistic and deterministic sensitivity analyses were presented separately for the 100mg and 200mg tildrakizumab doses. These indicated that both doses were cost-effective with similar results generated against the comparator sequences. In clinical practice it is expected that a specific proportion of the wider psoriasis population will receive the 100mg with the remainder receiving 200mg as per the SmPC which states that in patients with certain characteristics (e.g. high disease burden, body weight ≥90kg) 200mg may provide greater efficacy. The first three scenarios explore this further by combining the results of the 100mg and 200mg base case analyses. This has been achieved by generating results with both doses separately and then taking a weighted average of these results, based on the proportion of patients receiving the 200mg dose. Three scenarios were modelled to examine the following proportions of patients receiving the 200mg dose: [redacted] and [redacted].

A series of additional scenario analyses were undertaken to examine alternative assumptions for other model input parameters. For each of these scenarios, the results were based on a combined 100mg and 200mg population using the weighted average method described above (using parameters from scenario 2 – [redacted] of patients receiving 200mg). Further details of these scenarios are included below.

Scenario 1: tildrakizumab 200mg used in patients >90kg

The licence for tildrakizumab indicates that 200mg may provide greater efficacy for patients with a body weight of ≥90kg. Data from the reSURFACE trials indicates that [redacted] of the study population weighed >90kg.[41] Therefore, the results of the two base case analyses (100mg and 200mg) were weighted based on the assumption that [redacted] and [redacted] of patients would receive 200mg and 100mg doses respectively. The results are shown in Table 46.

Scenario 2: tildrakizumab 200mg used in patients with baseline PASI ≥20

The licence for tildrakizumab indicates that 200mg may provide greater efficacy for patients with a high disease burden. For the purpose of this scenario, this was defined as patients with a baseline PASI of ≥20. Data from the reSURFACE trials indicates that [redacted] of the study population had a PASI ≥20 at baseline.[41] Therefore, the results of the two base case analyses (100mg and 200mg) were weighted based on the assumption that [redacted] and [redacted] of patients would receive 200mg and 100mg doses respectively. The results are shown in Table 47.

Scenario 3: tildrakizumab 200mg used in patients >90kg and with baseline PASI ≥20

This scenario examined patients who had both a higher body weight and a high disease burden based on the criteria adopted for the two previous scenarios (i.e. >90kg and PASI ≥20 at baseline). Data from the reSURFACE trials indicates that [redacted] of the study population met both of these criteria.[41] Therefore, the results of the two base case analyses (100mg and 200mg) were weighted based on the assumption that [redacted] and [redacted] of patients would receive 200mg and 100mg doses respectively. The results are shown in Table 48.

Summary of scenario one to three results

Across all three scenarios the results were very similar. In all three scenarios tildrakizumab (sequence 1) was the referent comparator sequence 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 pairwise analysis also indicated that the tildrakizumab sequence generated a positive NMB versus each individual comparator sequence within all three scenarios, with only very minor changes in these values across the scenarios.

Overall, the results of these scenarios were very similar to the base case analysis and indicated that the proportion of patients receiving the 100mg and 200mg doses of tildrakizumab was not a key driver of the results. This was as expected given both of the doses were found to be cost-effective in the base case when examined separately.

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Table 46: Results of scenario 1: tildrakizumab 200mg used in patients >90kg

Sequence	Total costs	Total QALYs	Incremental costs (versus tildrakizumab)	Incremental QALYs (versus tildrakizumab)	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
1: Tildrakizumab	[redacted]	[redacted]				
5: Etanercept	£236,534	[redacted]	[redacted]	[redacted]	Dominated	£4,431
2: Adalimumab	£237,057	[redacted]	[redacted]	[redacted]	Dominated	£1,404
3: Ustekinumab	£237,820	[redacted]	[redacted]	[redacted]	Dominated	£2,155
4: Secukinumab	£245,955	[redacted]	[redacted]	[redacted]	Dominated	£10,125
6: Ixekizumab	£265,002	[redacted]	[redacted]	[redacted]	£165,795	£25,529
8: Guselkumab	£265,101	[redacted]	[redacted]	[redacted]	Dominated	£26,431
7: Brodalumab	£267,161	[redacted]	[redacted]	[redacted]	£4,806,207	£27,680

Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; N/A: not applicable; QALY: quality-adjusted life year.

Table 47: Results of scenario 2: tildrakizumab 200mg used in patients baseline PASI ≥20

Sequence	Total costs	Total QALYs	Incremental costs (versus tildrakizumab)	Incremental QALYs (versus tildrakizumab)	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
1: Tildrakizumab	[redacted]	[redacted]				
5: Etanercept	£236,533	[redacted]	[redacted]	[redacted]	Dominated	£4,397
2: Adalimumab	£237,057	[redacted]	[redacted]	[redacted]	Dominated	£1,373
3: Ustekinumab	£237,820	[redacted]	[redacted]	[redacted]	Dominated	£2,124
4: Secukinumab	£245,955	[redacted]	[redacted]	[redacted]	Dominated	£10,094
6: Ixekizumab	£265,004	[redacted]	[redacted]	[redacted]	£164,868	£25,499
8: Guselkumab	£265,100	[redacted]	[redacted]	[redacted]	Dominated	£26,400
7: Brodalumab	£267,165	[redacted]	[redacted]	[redacted]	£4,529,076	£27,650

Table 48: Results of scenario 3: tildrakizumab 200mg used in patients >90kg and baseline PASI ≥20

Sequence	Total costs	Total QALYs	Incremental costs (versus tildrakizumab)	Incremental QALYs (versus tildrakizumab)	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
1: Tildrakizumab	[redacted]	[redacted]				
5: Etanercept	£236,527	[redacted]	[redacted]	[redacted]	Dominated	£4,191
2: Adalimumab	£237,058	[redacted]	[redacted]	[redacted]	Dominated	£1,186
3: Ustekinumab	£237,821	[redacted]	[redacted]	[redacted]	Dominated	£1,937
4: Secukinumab	£245,953	[redacted]	[redacted]	[redacted]	Dominated	£9,904
6: Ixekizumab	£265,017	[redacted]	[redacted]	[redacted]	£159,480	£25,316
8: Guselkumab	£265,098	[redacted]	[redacted]	[redacted]	Dominated	£26,216
7: Brodalumab	£267,186	[redacted]	[redacted]	[redacted]	£3,364,742	£27,472

Scenario 4: increased mortality with psoriasis

In the base case analysis, it was assumed that there was no increased risk of mortality associated with moderate to severe plaque psoriasis. However, previous research indicates that mortality may be higher in the severe plaque psoriasis population, perhaps due to the presence of comorbid diseases, as shown by a HR of 1.42 (95% CI, 1.25 to 1.62) for severe psoriasis patients versus matched controls (Section B.3.3). In this scenario analysis, an assumed increase in mortality for plaque psoriasis was implemented by applying the hazard ratio of 1.42 to the general population mortality values.

Tildrakizumab (sequence 1) was the referent comparator sequence in the fully incremental analysis (Table 49). Ixekizumab (sequence 6) and brodalumab (sequence 7) were more costly and more effective than tildrakizumab (sequence 1), with ICERs of £167,001 and £4,451,529 per QALY, respectively. The other comparator sequences were dominated.

The pairwise analysis also indicated that the tildrakizumab sequence generated a positive NMB versus each individual comparator sequence.

Overall, the results of this scenario were very similar to the base case analysis. Due to the increased mortality rates in this scenario the total costs and QALYs were lower but the effect was largely equal on both treatment and comparator sequences. As such, only small changes in the ICERs occur. These changes were not significant enough to alter the conclusions of the analysis.

Table 49: Results of scenario 4: increased mortality with psoriasis

Sequence	Total costs	Total QALYs	Incremental costs (versus tildrakizumab)	Incremental QALYs (versus tildrakizumab)	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
1: Tildrakizumab	[redacted]	[redacted]	-	-	-	N/A
5: Etanercept	£224,854	[redacted]	[redacted]	[redacted]	Dominated	£4,327
2: Adalimumab	£225,361	[redacted]	[redacted]	[redacted]	Dominated	£1,356
3: Ustekinumab	£226,130	[redacted]	[redacted]	[redacted]	Dominated	£2,112
4: Secukinumab	£234,473	[redacted]	[redacted]	[redacted]	Dominated	£10,285
6: Ixekizumab	£253,165	[redacted]	[redacted]	[redacted]	£167,001	£25,408
8: Guselkumab	£253,245	[redacted]	[redacted]	[redacted]	Dominated	£26,278
7: Brodalumab	£255,277	[redacted]	[redacted]	[redacted]	£4,451,529	£27,510

Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; N/A: not applicable; QALY: quality-adjusted life year.

Scenario 5: alternative efficacy data for all comparators (28 weeks)

In the base case analysis, the time frame for treatment effectiveness data was 14 weeks. However, for all comparators follow-up data were also available for 28 weeks. Further, as described in Section B.3.3, there was evidence that tildrakizumab does not become fully effective until 28 weeks. Therefore, the 28 week effectiveness data have been applied for this scenario, based on the same NMA described previously, which also included an analysis of the 28 week data.

For inclusion in the model, the efficacy data at 14 weeks were applied at the end of the first cycle to assign patients into one of the four PASI health states. The 28 week data were then applied at the end of the second cycle to reassign people to one of the four health states. This allocation was then used to determine the proportion of patients who remained on treatment, thus moving into the maintenance period, and those who moved onto the next treatment based on the decision rule discussed previously (i.e. a PASI score of ≥75 is classified as an appropriate response). Essentially then, the induction period in the model was extended to 28 weeks for this particular scenario. The rest of the model was unchanged from the base case.

For this scenario, the lowest cost sequence, etanercept (sequence 5), was the referent comparator sequence in the fully incremental analysis (Table 50). For this analysis, tildrakizumab (sequence 1) was [redacted] effective and [redacted] costly then etanercept and associated with an ICER of £5,448. Brodalumab was also [redacted] effective and costly than both etanercept and tildrakizumab. Compared with tildrakizumab, the next treatment in the fully incremental analysis, it was associated with an ICER of £304,652. The piecewise analysis indicates that tildrakizumab is cost-effective versus each individual comparator sequence with a positive NMB value generated.

Following the adoption of the 28 week follow-up data, an overall improvement in the effectiveness of tildrakizumab results in a higher proportion of patients staying on treatment during the maintenance period. This results in higher overall costs for the tildrakizumab sequence hence it was no longer the lowest cost sequence. Nevertheless, as part of the fully incremental analysis it was the only sequence that produced an ICER of less than £30,000 per QALY and, therefore, was the most cost-effective option.

Table 50: Results of scenario 5: 28-week efficacy data

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
5: Etanercept	[redacted]	[redacted]	£0	0.00	-	£2,816
1: Tildrakizumab	£240,814	[redacted]	[redacted]	[redacted]	£5,448	
2: Adalimumab	£241,953	[redacted]	[redacted]	[redacted]	Dominated	£2,253
3: Ustekinumab	£242,886	[redacted]	[redacted]	[redacted]	Dominated	£3,173
4: Secukinumab	£252,724	[redacted]	[redacted]	[redacted]	Dominated	£12,803
6: Ixekizumab	£273,548	[redacted]	[redacted]	[redacted]	Dominated	£30,586
7: Brodalumab	£273,925	[redacted]	[redacted]	[redacted]	£304,652	£31,080
8: Guselkumab	£274,916	[redacted]	[redacted]	[redacted]	Dominated	£32,614

Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; QALY: quality-adjusted life year.

Scenario 6: relative risk of 1 when insignificant (for efficacy data)

In the base case analysis, the relative risk ratios used to determine the effectiveness of each comparator were derived from the NMA. This was not dependent upon whether the confidence intervals indicated significance. However, compared with certain interventions, the difference between tildrakizumab and the comparator was insignificant (i.e. the 95% confidence interval crossed 1) for certain outcome measures, which indicates that the difference in effectiveness shown by the NMA may have occurred due to chance (at the 95% level). Therefore, in this scenario analysis, relative risks were set to 1 if the confidence intervals associated with the relative risk crossed 1 to examine the impact on the results.

Tildrakizumab (sequence 1) was the referent comparator sequence in the incremental analysis (Table 51). Etanercept (sequence 5) and guselkumab (sequence 8) were the only dominated comparators for the incremental analysis. Secukinumab (sequence 4) was also extendedly dominated as it was associated with an ICER of £1,019,887 and this was higher than the ICER of ixekizumab (£113,973), which was a more effective treatment option.

Compared with adalimumab (sequence 2) and ustekinumab (sequence 3), tildrakizumab was equally effective so there was no difference in the QALYs generated by each treatment. However, tildrakizumab was cost saving versus both treatments with an incremental cost of [redacted] and [redacted] compared with adalimumab and ustekinumab respectively.

Ixekizumab (sequence 6) and brodalumab (sequence 7) were both [redacted] costly and [redacted] effective than tildrakizumab and were associated with ICERs of £113,973 and £4,529,076 respectively.

The piecewise analysis indicates that tildrakizumab is cost-effective versus each individual comparator sequence with a positive NMB value generated.

Overall, the results of this scenario analysis are similar to the base case analysis. All of the comparator sequences were either dominated, extendedly dominated or more costly (with equal efficacy) within the fully incremental analysis, and thus would not be considered as cost-effective, with the exception of ixekizumab and brodalumab (sequences 6 and 7 respectively). However, the ICER for these sequences were £113,973 and £4,529,076 respectively, which are far greater than the cost-effectiveness threshold of £20,000 to £30,000 and, therefore, the tildrakizumab sequence is the most cost-effective option.

Table 51: Results of scenario 6: relative risk of 1 when difference insignificant (efficacy data)

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
1: Tildrakizumab	[redacted]	[redacted]	£0	0.00	-	N/A
5: Etanercept	£236,633	[redacted]	[redacted]	[redacted]	N/A	£4,408
2: Adalimumab	£236,963	[redacted]	[redacted]	[redacted]	N/A	£883
3: Ustekinumab	£237,734	[redacted]	[redacted]	[redacted]	N/A	£1,654
4: Secukinumab	£245,902	[redacted]	[redacted]	[redacted]	Extendedly Dominated	£9,662
6: Ixekizumab	£265,906	[redacted]	[redacted]	[redacted]	£113,973	£25,487
8: Guselkumab	£265,193	[redacted]	[redacted]	[redacted]	Dominated	£26,391
7: Brodalumab	£267,256	[redacted]	[redacted]	[redacted]	£4,529,076	£27,639

Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; N/A: not applicable; QALY: quality-adjusted life year.

Scenario 7: single treatment comparator

An incremental analysis was undertaken based on sequences in which treatment was followed immediately by BSC. For example: tildrakizumab > BSC > BSC > BSC.

The results of this scenario are presented in Table 52. Tildrakizumab (sequence 1) was the referent comparator sequence in the fully incremental analysis as it was associated with the lowest total cost (Table 52). Two sequences were dominated by tildrakizumab (adalimumab and etanercept, sequences 2 and 5 respectively) whilst guselkumab (sequence 8) was also dominated. Ustekinumab (sequence 3) and secukinumab (sequence 4) were both extendedly dominated by ixekizumab as this sequence was more effective and also associated with a lower ICER. Therefore, two comparator sequences, ixekizumab (sequence 6) and brodalumab (sequence 7) were not dominated or extendedly dominated but associated with ICERs of £136,626 and £4,529,076 respectively.

The piecewise analysis indicates that tildrakizumab was cost-effective versus each individual comparator sequence with a positive NMB value generated.

Overall, the results of this scenario were similar to the base case analysis with all of the comparator sequences being either dominated or extendedly dominated within the fully incremental analysis except ixekizumab and brodalumab (sequences 6 and 7 respectively). The ICERs for ixekizumab and brodalumab are far greater than the cost-effectiveness threshold of £20,000 to £30,000 and, therefore, the tildrakizumab sequence is the most cost-effective option.

Table 52: Results of scenario 7: single treatment comparator

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
1: Tildrakizumab	[redacted]	[redacted]	£0	0.00	-	N/A
5: Etanercept	£225,182	[redacted]	[redacted]	[redacted]	Dominated	£4,800
2: Adalimumab	£226,208	[redacted]	[redacted]	[redacted]	Dominated	£1,404
3: Ustekinumab	£228,195	[redacted]	[redacted]	[redacted]	Extendedly Dominated	£2,831
4: Secukinumab	£253,200	[redacted]	[redacted]	[redacted]	Extendedly Dominated	£24,569
8: Guselkumab	£254,646	[redacted]	[redacted]	[redacted]	Dominated	£26,138
6: Ixekizumab	£254,651	[redacted]	[redacted]	[redacted]	£136,626	£25,161
7: Brodalumab	£256,812	[redacted]	[redacted]	[redacted]	£4,529,076	£27,312

Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; N/A: not applicable; QALY: quality-adjusted life year.

Scenario 8: Best supportive care costs

In the base case analysis, the cost of BSC was determined by the NICE clinical guideline for psoriasis assessment and management (CG 153).[5] However, as described previously, there is a degree of uncertainty regarding the true annual cost of BSC in this indication. The study by Fonia and colleagues has commonly been used in previous NICE appraisals in this indication and, therefore, resource use data from this study was applied for this scenario based on information reported in the brodalumab submission.[23] This resulted in the cost per cycle of BSC being reduced from £3,088 to £1,422.

Etanercept (sequence 5) was the referent comparator sequence in the fully incremental analysis (Table 53). Tildrakizumab (sequence 1) was associated with an ICER of £22,126 versus etanercept (sequence 5). The only sequences that were not dominated or extendedly dominated were ixekizumab (sequence 6) and brodalumab (sequence 7), which were associated with final ICERs of £187,881 and £4,529,076 respectively.

When compared pairwise to each treatment sequence, tildrakizumab (sequence 1) was associated with INMBs ranging from -£490 versus etanercept (sequence 5) to £31,701 versus brodalumab (sequence 7).

Overall, the implementation of BSC costs from Fonia and colleagues has reduced the pairwise INMBs for tildrakizumab compared with sequences two to five, whilst causing an increase in the INMB when compared with sequences six to eight. This is the first scenario in which tildrakizumab would not be considered cost-effective at a threshold of £20,000 per QALY because, for the fully incremental analysis, the ICER of tildrakizumab versus etanercept is above £20,000. Therefore, etanercept would have been the most cost-effective option, although given the proximity of the ICER to the threshold value the two treatments were close to equivalence.

Table 53: Results of scenario 8: Best supportive care costs

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
5: Etanercept	£165,118	[redacted]	£0	0.00	-	-£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

Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; QALY: quality-adjusted life year.

Scenario 9: Alternative discontinuation data

Egeberg and colleagues report data on drug survival for four of the biologic therapies included in the analysis (adalimumab, etanercept, secukinumab and ustekinumab) based on data from the Danish Biologic Interventions Registry (DERMBIO).[114] This registry contains data on all patients receiving biologic therapies (or biosimilars) for moderate to severe plaque psoriasis with data collection mandatory from 2007. Egeberg et al report data for a total of 2,161 patients from 1st January 2007 until 31st March 2017.[114]

Whilst these data are from a non-UK setting it is expected they would still be generalisable and, therefore, the adoption of data was explored as part of this scenario. UK-specific data are also available, based on BADBIR, but published reports cover a shorter time horizon and do not currently include secukinumab, hence the DERMBIO data were favoured here.

For the scenario analysis, we used the same technical approach to generating annual discontinuation rates in combination with the drug survival data for each of the four drugs reported by Egeberg et al were taken and a separate exponential curve was fitted for each treatment. Data were reported from treatment initiation but the first four months of data were excluded from the curve fitting as the discontinuations during this period will already be captured within the model for the patients who switch treatments at the end of the induction period due to a lack of response.

Based on the exponential curves that were fitted for each treatment, the exponential coefficient was used to determine the constant annual probability of discontinuation with these values subsequently applied within the model for the four treatments with available data. These probabilities were as follows:

- Adalimumab = 8.20%
- Etanercept = 16.10%
- Secukinumab = 7.90%
- Ustekinumab = 7.90%

It should be noted that based on the exponential curves that were fitted to the DERMBIO data for secukinumab an annual discontinuation rate of 49% was generated, which was substantially higher than the other IL-inhibitor with data, ustekinumab. The discrepancy was corrected by conservatively assuming that the rate estimated for ustekinumab (i.e. 7.9%) was also valid for secukinumab and thus this value was applied for secukinumab in the scenario.

For the remaining treatments in the analysis (i.e. tildrakizumab, ixekizumab, brodalumab and guselkumab) no registry data were identified. All of these treatments are IL-inhibitors, the same as secukinumab and ustekinumab (as opposed to adalimumab and etanercept, which are anti-TNF inhibitors). Therefore it was assumed the efficacy of the remaining treatments would more closely match the other IL-inhibitors and the registry data. Given the large difference between discontinuation rates for ustekinumab and secukinumab, the lower rates observed for ustekinumab were applied to all remaining treatments, including tildrakizumab.

Tildrakizumab (sequence 1) was the referent comparator sequence in the fully incremental analysis as it was associated with the lowest total cost. Only two of the sequences were not dominated in the fully incremental analysis. These were the sequences for ixekizumab and brodalumab, which were associated with ICERs of £217,927 and £11,021,874 respectively.

The results of the analysis are shown in Table 54 and are very similar to the base case analysis with the tildrakizumab sequence proving to be the most cost-effective option at a cost-effectiveness threshold of £20,000 per QALY.

Table 54: Results of scenario 9: alternative discontinuation data

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
1: Tildrakizumab	[redacted]	[redacted]	£0	0	-	N/A
2: Adalimumab	£230,787	[redacted]	[redacted]	[redacted]	Dominated	£4,185
3: Ustekinumab	£231,856	[redacted]	[redacted]	[redacted]	Dominated	£5,247
5: Etanercept	£236,517	[redacted]	[redacted]	[redacted]	Dominated	£16,667
4: Secukinumab	£255,237	[redacted]	[redacted]	[redacted]	Dominated	£28,113
6: Ixekizumab	£276,682	[redacted]	[redacted]	[redacted]	£217,927	£44,934
8: Guselkumab	£280,186	[redacted]	[redacted]	[redacted]	Dominated	£49,490
7: Brodalumab	£286,544	[redacted]	[redacted]	[redacted]	£11,021,874	£54,778

Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; QALY: quality-adjusted life year.

Scenario 10: Alternative utility data

As described in Section B.3.4, there are numerous other sources for utility data, particularly from previous submissions to NICE in this indication. Therefore, a scenario was run by which utility values were based on data available from the previous studies that also met the format of the model structure (i.e. separation by PASI response; see Table 32). For the purpose of this analysis, mean values, presented as crude averages (i.e. the proportion of patients that informed the underlying studies was not accounted for), were generated from these previous studies. These values are presented in Table 55 and show consistency with those values adopted for the base case analysis. As with the values adopted in the base case analysis the values were adjusted to account for the general decline in utility as the model population ages.

Table 55: Summary of alternative utility values sourced from the wider literature, DLQI >10

State	Utility from base case	Utility for scenario 10	Source
Baseline	0.61	0.61	Mean values calculated based on the values reported in Table 32
PASI score: <50	0.67	0.66	
PASI score: ≥50 to <75	0.83	0.79	
PASI score: ≥75 to <90	0.85	0.84	
PASI score: ≥90	0.89	0.88	

Abbreviations: PASI: Psoriasis Area Severity Index

Tildrakizumab (sequence 1) was the referent comparator sequence in the fully incremental analysis as it was associated with the lowest total cost. Only two of the sequences were not dominated in the fully incremental analysis. These were the sequences for ixekizumab and brodalumab, which were associated with ICERs of £217,927 and £11,021,874 respectively.

The piecewise analysis indicates that tildrakizumab was cost-effective versus each individual comparator sequence with a positive NMB value generated.

The results of the analysis are shown in Table 56 and are very similar to the base case analysis with the tildrakizumab sequence proving to be the most cost-effective option at a cost-effectiveness threshold of £20,000 per QALY.

Table 56: Results of scenario 10: alternative utility data

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
1: Tildrakizumab	[redacted]	[redacted]	£0	0	-	N/A
5: Etanercept	£236,533	[redacted]	[redacted]	[redacted]	Dominated	£4,542
2: Adalimumab	£237,057	[redacted]	[redacted]	[redacted]	Dominated	£1,386
3: Ustekinumab	£237,820	[redacted]	[redacted]	[redacted]	Dominated	£2,135
4: Secukinumab	£245,955	[redacted]	[redacted]	[redacted]	Dominated	£10,082
6: Ixekizumab	£265,004	[redacted]	[redacted]	[redacted]	£156,872	£25,320
8: Guselkumab	£265,100	[redacted]	[redacted]	[redacted]	Dominated	£26,265
7: Brodalumab	£267,165	[redacted]	[redacted]	[redacted]	£3,969,537	£27,470

Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; QALY: quality-adjusted life year.

Summary of sensitivity analyses results

The probabilistic results generated were similar to the base case analysis with the majority of sequences being either dominated or extendedly dominated by the tildrakizumab sequence, which was the most cost-effective option based on a threshold of £20,000 to £30,000 per QALY.

The DSA results show that the model results were relatively robust to changes in the input parameters, particularly for the pairwise comparisons of the tildrakizumab sequence to the ixekizumab, brodalumab and guselkumab sequences as the direction of the results did not change (i.e. the INMB did not cross £0 at threshold of £20,000 per QALY) in any instance, with the exception of the unit cost of tildrakizumab (and only if the price were increased by close to [redacted]). In general, the model results were most sensitive to changes in the unit cost of tildrakizumab as indicated by the fact that the direction of the results changed when these parameters were altered by [redacted] for the pairwise analyses with the other four comparator sequences. Changes to the following parameters also had a significant impact on the results for up to three of the pairwise analyses: discontinuation rate with tildrakizumab, discontinuation rate with adalimumab, rate of PASI 75 score with tildrakizumab and rate of PASI 75 score with adalimumab.

The results of the scenario analyses are summarised in Table 57. Overall, the results of the scenario analyses indicate that the results of the base case analysis are robust as the changes implemented as part of these scenarios had a very limited impact on the overall results. There was scenario in which tildrakizumab was not the most cost-effective sequence and this occurred when the cost of the best supportive care was substantially reduced (Scenario 8, Table 53). When this change was implemented the etanercept sequence was cost-effective at a £20,000 per QALY threshold but only by a small margin and if the threshold is increased to £30,000 the tildrakizumab sequence would then become cost-effective. Nevertheless, this does indicate that the cost of best supportive care is an important driver of the overall results.

Table 57: Summary of scenario analyses

Scenario number	Feature assessed	Overview of the scenario	Conclusion
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.
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.
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.
6	Alternative 14 week effectiveness 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.
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.
8	BSC cost	Data from Fonia *et al.* used to estimate cost of BSC	Etanercept sequence became the most cost-effective option but with only a small difference compared with tildrakizumab.
9	Discontinuation	Different annual rates of discontinuation applied based on DERMBIO registry data	Limited change from base case with the tildrakizumab sequence the most cost-effective option.
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.

Abbreviations: BSC: best supportive care.

B.3.9 Subgroup analysis

Section B.3.8.4 pages 134 -7 describes scenario analyses which explore differing proportions of patients using 100 / 200mg tildrakizumab based on patient characteristics.

B.3.10 Validation

Validation of cost-effectiveness analysis

The internal validity of the model was examined via a two-step process. Firstly, a cell-by-cell check of all model formulae was undertaken to ensure they were both correct and appropriately applied. Secondly, a model verification checklist was used,

which includes a range of tests, including sense checks, for instance, changing certain inputs to zero and checking that the observed effect was as expected (i.e. illogical results were not generated). This internal validation process was undertaken by a health economist who was not directly involved in the conceptualisation and development of the model.

The face validity of the model was also examined during the UK Advisory Board. This was achieved by describing the model structure and inputs to UK clinical experts to ensure the suggested approach appropriately captured costs and outcomes for UK clinical practice. Specific revisions were made to the model upon the advice received.[87]

External validity of the model was also examined by comparing the results of the previous economic evaluations in this indication. A number of relevant cost-effectiveness models are available, as discussed previously. However, due to differences in the modelling approaches, the results of these previously analyses are not directly applicable to this analysis, in particular: treatments considered (i.e. not tildrakizumab), time horizon, utility data and approach to the costing of BSC so such a validation check was not possible.

B.3.11 Interpretation and conclusions of economic evidence

The economic evaluation considered patients with moderate to severe plaque psoriasis. This reflects the population of the two reSURFACE studies in which the efficacy of tildrakizumab was assessed (section B.2) and reflects the population included in the final NICE scope.

It is expected the results of the economic evaluation are generalisable to clinical practice in England, for the following reasons:

- The structure of the economic model is consistent with previous submissions to NICE in this indication.
- The population of the reSURFACE studies are considered to be reflective of the patient population in England and Wales.
- Unit costs have been sourced from relevant, well-established UK sources (e.g. NHS Reference Costs, PSSRU, BNF).

- The approach adopted takes into account feedback from the ERGs and Appraisal Committees in previous NICE psoriasis appraisals.
- The model structure and inputs have been validated by UK-based clinical experts.[87]

A key strength of the economic evaluation is that the efficacy of each intervention is based on an extensive NMA that connects a number of large-scale RCTs. Therefore robust estimates of treatment effects are included in the economic model.

The main weakness of the economic evaluation is that a small number of simplifying assumptions were required, largely due to an absence of relevant data. In particular, it was assumed that a treatment's position in each sequence did not impact its efficacy, the impact of each treatment was sustained during the treatment maintained period and the rate of discontinuation was constant and equal across all interventions. However, these assumptions have been consistently applied in all previous submissions in this indication.

Overall the results of the economic evaluation indicate that tildrakizumab is a cost-effective treatment option for patients with moderate to severe plaque psoriasis when compared with other biologic therapies currently available for patients in England and Wales.

Two base case analyses were completed to examine the cost-effectiveness of both tildrakizumab doses (i.e. 100mg and 200mg). The results of these analyses were very similar and indicate that in fully incremental analyses in which all comparator sequences were compared to the tildrakizumab sequence (as the tildrakizumab sequence was associated with the lowest costs), the tildrakizumab sequence dominated all except two of the comparator sequences. The two non-dominated sequences were led by ixekizumab and brodalumab and these were associated with ICERs of at least £150,000 and £2,800,000 respectively (brodalumab was dominated for the 200mg base case analysis). These are substantially higher than the range normally deemed acceptable by NICE (i.e. £20,000 to £30,000 per QALY). The tildrakizumab sequence was therefore the most cost-effective sequence. This conclusion was also broadly supported by the outputs for the sensitivity and scenario analyses.

B.4 References

1. Almirall. *Ilumetri Summary of Product Characteristics (Draft July 2018) (Commercial in Confidence).*
2. National Institute for Health and Care Excellence Clinical Guideline 153: Psoriasis: Assessment and management. October 2012; www.nice.org.uk/guidance/cg153. Accessed August 2018.
3. British Association of Dermatologists Patient Information Leaflet: Topical treatment for psoriasis. Update August 2017; http://www.bad.org.uk/for-the-public/patient-information-leaflets. Accessed August 2018.
4. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM, team IaMoPaACIp. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol.* 2013;133(2):377-385.
5. National Institute for Health and Care Excellence Clinical Guideline 153: Psoriasis: Assessment and management. Costing Report. October 2012; www.nice.org.uk/guidance/cg153. Accessed August 2018.
6. Di Meglio P, Villanova F, Nestle FO. Psoriasis. *Cold Spring Harb Perspect Med.* 2014;4(8).
7. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2008;58(5):826-850.
8. British Association of Dermatologists Patient Information Leaflet: Psoriasis - an overview. Update September 2015; www.bad.org.uk/for-the-public/patient-information-leaflets. Accessed August 2018.
9. Boehncke WH, Schön MP. Psoriasis. *Lancet.* 2015;386(9997):983-994.
10. Pathirana D, Ormerod AD, Saiag P, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol.* 2009;23 Suppl 2:1-70.
11. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. *Ann Rheum Dis.* 2005;64 Suppl 2:ii18-23; discussion ii24-15.
12. Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. *Arch Dermatol.* 2001;137(3):280-284.
13. Kimball AB, Jacobson C, Weiss S, Vreeland MG, Wu Y. The psychosocial burden of psoriasis. *Am J Clin Dermatol.* 2005;6(6):383-392.
14. Lewis-Beck C, Abouzaid S, Xie L, Baser O, Kim E. Analysis of the relationship between psoriasis symptom severity and quality of life, work productivity, and activity impairment among patients with moderate-to-severe psoriasis using structural equation modeling. *Patient Prefer Adherence.* 2013;7:199-205.
15. World Health Organisation global report on psoriasis. 2016; http://apps.who.int/iris/bitstream/10665/204417/1/9789241565189_eng.pdf. Accessed August 2018.
16. National Institute for Health and Care Excellence pathway for psoriasis. Updated September 2017; http://pathways.nice.org.uk/pathways/psoriasis. Accessed August 2018.
17. Lebwohl M, Ting PT, Koo JY. Psoriasis treatment: traditional therapy. *Ann Rheum Dis.* 2005;64 Suppl 2:ii83-86.
18. National Institute for Health and Care Excellence Technology Appraisal 103: Etanercept and efalizumab for the treatment of adults with psoriasis. 26 July 2006 www.nice.org.uk/guidance/ta103. Accessed August 2018.
19. National Institute for Health and Care Excellence Technology Appraisal 146: Adalimumab for the treatment of adults with psoriasis. 25 June 2008; www.nice.org.uk/guidance/ta146. Accessed August 2018.

20. National Institute for Health and Care Excellence Technology Appraisal 180: Ustekinumab for the treatment of adults with moderate to severe psoriasis. 23 September 2009 www.nice.org.uk/guidance/ta180. Accessed August 2018.
21. National Institute for Health and Care Excellence Technology Appraisal 350: Secukinumab for treating moderate to severe plaque psoriasis. 22 July 2015; www.nice.org.uk/guidance/ta350. Accessed August 2018.
22. National Institute for Health and Care Excellence Technology Appraisal 442: Ixekizumab for treating moderate to severe plaque psoriasis. 26 April 2017; www.nice.org.uk/guidance/ta442. Accessed August 2018.
23. National Institute for Health and Care Excellence Technology Appraisal 511: Brodalumab for treating moderate to severe plaque psoriasis. 21 March 2018; www.nice.org.uk/guidance/ta511. Accessed August 2018.
24. National Institute for Health and Care Excellence Technology Appraisal 134: Infliximab for the treatment of adults with psoriasis. 23 January 2008; www.nice.org.uk/guidance/ta134. Accessed August 2018.
25. National Institute for Health and Care Excellence Technology Appraisal 521: Guselkumab for treating moderate to severe plaque psoriasis. 13 June 2018; www.nice.org.uk/guidance/ta521. Accessed August 2018.
26. Smith CH, Jabbar-Lopez ZK, Yiu ZZ, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. *Br J Dermatol.* 2017;177(3):628-636.
27. Belinchón I, Rivera R, Blanch C, Comellas M, Lizán L. Adherence, satisfaction and preferences for treatment in patients with psoriasis in the European Union: a systematic review of the literature. *Patient Prefer Adherence.* 2016;10:2357-2367.
28. Zhang M, Brenneman SK, Carter CT, et al. Patient-reported treatment satisfaction and choice of dosing frequency with biologic treatment for moderate to severe plaque psoriasis. *Patient Prefer Adherence.* 2015;9:777-784.
29. Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. *JAMA Dermatol.* 2013;149(10):1180-1185.
30. Warren RB, Smith CH, Yiu ZZN, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol.* 2015;135(11):2632-2640.
31. Menter A, Papp KA, Gooderham M, et al. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Eur Acad Dermatol Venereol.* 2016;30(7):1148-1158.
32. Galluzzo M, D'adamio S, Bianchi L, Talamonti M. Tildrakizumab for treating psoriasis. *Expert Opin Biol Ther.* 2017;17(5):645-657.
33. Bartlett HS, Million RP. Targeting the IL-17-T(H)17 pathway. *Nat Rev Drug Discov.* 2015;14(1):11-12.
34. National Institute for Health and Care Excellence guide to the methods of technology appraisal. 2013; www.nice.org.uk/process/pmg9. Accessed August 2018.
35. Papp K, Thaçi D, Reich K, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol.* 2015;173(4):930-939.
36. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet.* 2017;390(10091):276-288.
37. *Clinical study report for MK-3222 P010 (reSURFACE 1): A 64-week, phase 3, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed*

by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (Commercial in Confidence). 13 February 2017.
38. *Clinical study report for MK-3222 P011 (reSURFACE 2): A 52-week, phase 3, randomized, active comparator and placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to–severe chronic plaque psoriasis (Commercial in Confidence).* 22 February 2017.
39. The Cochrane Risk of Bias Tool: Assessing risk of bias in included studies. http://methods.cochrane.org/bias/assessing-risk-bias-included-studies. Accessed August 2018.
40. Almirall. *Data on file (2). Long term data (Commercial in Confidence).* August 2018.
41. Almirall. *Data on file (1). Subgroup data (Commercial in Confidence).* August 2018.
42. Griffiths CEM, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *New England Journal of Medicine.* 2010;362(2):118-128.
43. Papp KA, Reich K, Paul C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *British Journal of Dermatology.* 2016;175(2):273-286.
44. Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with utekinumab in psoriasis. *New England Journal of Medicine.* 2015;373(14):1318-1328.
45. Strober B, Langley R, Blicharski T, et al. AMAGINE-3: a phase 3 efficacy and safety study to evaluate induction and maintenance regimens of brodalumab compared with placebo and ustekinumab in patients with moderate to severe plaque psoriasis. 23rd World Congress of Dermatology; 8-13 June, 2015; Vancouver, Canada.
46. Asahina A, Nakagawa H, Etoh T, Ohtsuki M, Adalimumab MSG. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a phase II/III randomized controlled study. *J Dermatol.* 2010;37(4):299-310.
47. Bissonnette R, Tardif J-C, Harel F, Pressacco J, Bolduc C, Guertin M-C. Effects of the tumor necrosis factor-alpha antagonist adalimumab on arterial inflammation assessed by positron emission tomography in patients with psoriasis: results of a randomized controlled trial. *Circ Cardiovasc Imaging.* 2013;6(1):83-90.
48. Mrowietz U, Szepietowski JC, Loewe R, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm- and placebo-controlled trial (BRIDGE). *British Journal of Dermatology.* 2017;176(3):615-623.
49. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *British Journal of Dermatology.* 2008;158(3):558-566.
50. Thaci D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *Journal of the American Academy of Dermatology.* 2015;73(3):400-409.
51. Papp K, Cather JC, Rosoph L, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *The Lancet.* 2012;380(9843):738-746.
52. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *New England Journal of Medicine.* 2014;371(4):326-338.
53. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (efficacy and safety trial evaluating the effects

of apremilast in psoriasis [ESTEEM] 1). *Journal of the American Academy of Dermatology.* 2015;73(1):37-49.
54. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *British Journal of Dermatology.* 2015;173(6):1387-1399.
55. Blauvelt A, Prinz JC, Gottlieb AB, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). *British Journal of Dermatology.* 2015;172(2):484-493.
56. Gottlieb AB, Matheson RT, Lowe N, et al. A randomized trial of etanercept as monotherapy for psoriasis. *Archives of Dermatology.* 2003;139(12):1627-1632.
57. Igarashi A, Kato T, Kato M, Song M, Nakagawa H. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. *J Dermatol.* 2012;39(3):242-252.
58. Paul C, Lacour JP, Tedremets L, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). *Journal of the European Academy of Dermatology & Venereology.* 2015;29(6):1082-1090.
59. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *New England Journal of Medicine.* 2003;349(21):2014-2022.
60. Reich K, Gooderham M, Green L, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). *Journal of the European Academy of Dermatology & Venereology.* 2017;31(3):507-517.
61. Zhu X, Zheng M, Song M, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). *Journal of Drugs in Dermatology.* 2013;12(2):166-174.
62. Gordon KB, Langley RG, Leonardi C, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *Journal of the American Academy of Dermatology.* 2006;55(4):598-606.
63. Nakagawa H, Niiro H, Ootaki K, Japanese brodalumab study g. Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: efficacy and safety results from a phase II randomized controlled study. *J Dermatol Sci.* 2016;81(1):44-52.
64. Ohtsuki M, Okubo Y, Komine M, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of Japanese patients with moderate to severe plaque psoriasis: efficacy, safety and tolerability results from a phase 2b randomized controlled trial. *J Dermatol.* 2017;44(8):873-884.
65. Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *British Journal of Dermatology.* 2005;152(6):1304-1312.
66. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *New England Journal of Medicine.* 2012;366(13):1181-1189.
67. Tsai T-F, Ho J-C, Song M, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *J Dermatol Sci.* 2011;63(3):154-163.
68. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet.* 2008;371(9625):1665-1674.
69. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week

results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet.* 2008;371(9625):1675-1684.
70. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol.* 2008;58(1):106-115.
71. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet.* 2006;367(9504):29-35.
72. Abbvie. Risankizumab meets all co-primary and ranked secondary endpoints, achieving significantly greater efficacy versus standard biologic therapies in three pivotal phase 3 psoriasis studies. [webpage]. 2017; https://news.abbvie.com/news/press-releases/risankizumab-meets-all-co-primary-and-ranked-secondary-endpoints-achieving-significantly-greater-efficacy-versus-standard-biologic-therapies-in-three-pivotal-phase-3-psoriasis-studies.htm. Accessed August 2018.
73. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *New England Journal of Medicine.* 2016;375(4):345-356.
74. Griffiths CEM, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet.* 2015;386(9993):541-551.
75. Celgene. Study of the efficacy and safety of apremilast (CC-10004), in subjects with moderate plaque psoriasis. *ClinicalTrials.gov* 2015; NCT02555826:https://clinicaltrials.gov/show/NCT02555826. Accessed August 2018.
76. van de Kerkhof PCM, Segaert S, Lahfa M, et al. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. *British Journal of Dermatology.* 2008;159(5):1177-1185.
77. Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *Journal of the American Academy of Dermatology.* 2017;76(3):405-417.
78. Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol.* 2017;76(3):418-431.
79. Gordon KB, Duffin KC, Bissonnette R, et al. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. *New England Journal of Medicine.* 2015;373(2):136-144.
80. Cai L, Gu J, Zheng J, et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. *Journal of the European Academy of Dermatology & Venereology.* 2017;31(1):89-95.
81. Blauvelt A, Reich K, Papp KA, et al. Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials. *Br J Dermatol.* 2018.
82. Sun Pharma Global FZE. A Study to Evaluate the Efficacy and Safety of Subcutaneous MK-3222, Followed by an Optional Long-Term Safety Extension Study, in Participants With Moderate-to-Severe Chronic Plaque Psoriasis (MK-3222-010) (reSURFACE 1). *ClinTrials.gov* 2012; NCT01722331:https://clinicaltrials.gov/ct2/show/NCT01722331 Accessed August 2018.

83. Sun Pharma Global FZE. A Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222) in Participants With Moderate-to-Severe Chronic Plaque Psoriasis Followed by a Long-term Extension Study (MK-3222-011) (reSURFACE 2). *ClinTrials.gov* 2012; NCT01729754:https://clinicaltrials.gov/ct2/show/NCT01729754. Accessed August 2018.
84. Sun Pharma Global FZE. A Long Term Study to Demonstrate the Safety and Efficacy of Tildrakizumab in Subjects With Psoriatic Arthritis and Ankylosing Spondylitis or Non-Radiographic Axial Spondyloarthritis. *ClinTrials.gov* 2018; NCT03552276:https://clinicaltrials.gov/ct2/show/study/NCT03552276. Accessed August 2018.
85. Guerriero F, Orlando V, Monetti VM, Russo V, Menditto E. Biological therapy utilization, switching, and cost among patients with psoriasis: retrospective analysis of administrative databases in Southern Italy. *Clinicoecon Outcomes Res.* 2017;9:741-748.
86. Tian HG, I. Mollon, P. McDwyer, P. Lotya J. Biologics Switching Patterns and Associated Costs in Psoriasis Patients in a Large Commercially Insured Population in the United States. *Value in Health.* 2016;19(3):Page A125
87. Almirall. *Data on file. Summary report. Tildrakizumab advisory board (Commercial in Confidence).* March 2018.
88. Kim WB, Marinas JE, Qiang J, Shahbaz A, Greaves S, Yeung J. Adverse events resulting in withdrawal of biologic therapy for psoriasis in real-world clinical practice: A Canadian multicenter retrospective study. *J Am Acad Dermatol.* 2015;73(2):237-241.
89. Yiu ZZN, Smith CH, Ashcroft DM, et al. Risk of Serious Infection in Patients with Psoriasis Receiving Biologic Therapies: A Prospective Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol.* 2018;138(3):534-541.
90. Saunte DM, Mrowietz U, Puig L, Zachariae C. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. *Br J Dermatol.* 2017;177(1):47-62.
91. Henderson Berg MH, Carrasco D. Injection Site Reactions to Biologic Agents Used in Psoriasis and Psoriatic Arthritis. *J Drugs Dermatol.* 2017;16(7):695-698.
92. Sârbu MT, M. Mitran, MI. Mitran, CI. Limbău, AM. Georgescu, SR. Adverse reactions of biological therapies in patients with psoriasis. *J Mind Med Sci.* 2017;4(1):4-12.
93. Feldman SR, Zhao Y, Navaratnam P, Friedman HS, Lu J, Tran MH. Patterns of medication utilization and costs associated with the use of etanercept, adalimumab, and ustekinumab in the management of moderate-to-severe psoriasis. *J Manag Care Spec Pharm.* 2015;21(3):201-209.
94. Etanercept Summary of Product Characteristics. www.medicines.org.uk/emc/product/8117/smpc. Accessed August 2018.
95. Puzenat E, Bronsard V, Prey S, et al. What are the best outcome measures for assessing plaque psoriasis severity? A systematic review of the literature. *J Eur Acad Dermatol Venereol.* 2010;24 Suppl 2:10-16.
96. Ustekinumab Summary of Product Characteristics. www.medicines.org.uk/emc/product/7639/smpc. Accessed August 2018.
97. Duffin KC, Yeung H, Takeshita J, et al. Patient satisfaction with treatments for moderate-to-severe plaque psoriasis in clinical practice. *Br J Dermatol.* 2014;170(3):672-680.
98. Korman NJ, Zhao Y, Pike J, Roberts J. Relationship between psoriasis severity, clinical symptoms, quality of life and work productivity among patients in the USA. *Clin Exp Dermatol.* 2016;41(5):514-521.

99. Mustonen A, Mattila K, Leino M, Koulu L, Tuominen R. How much of the productivity losses among psoriasis patients are due to psoriasis. *BMC Health Serv Res.* 2015;15:87.
100. Joint Formulary Committee. British National Formulary . Edition number 75. London: BMJ Group and Pharmaceutical Press. 2018; https://bnf.nice.org.uk/.
101. Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. *Br J Dermatol.* 2015;172(1):244-252.
102. Inzinger M, Wippel-Slupetzky K, Weger W, et al. Survival and Effectiveness of Tumour Necrosis Factor-alpha Inhibitors in the Treatment of Plaque Psoriasis under Daily Life Conditions: Report from the Psoriasis Registry Austria. *Acta Dermato-Venereologica.* 2016;96(2):207-212.
103. Menting SP, Sitaram AS, Bonnerjee-van der Stok HM, de Rie MA, Hooft L, Spuls PI. Drug survival is not significantly different between biologics in patients with psoriasis vulgaris: a single-centre database analysis. *British Journal of Dermatology.* 2014;171(4):875-883.
104. van den Reek JM, Zweegers J, Kievit W, et al. 'Happy' drug survival of adalimumab, etanercept and ustekinumab in psoriasis in daily practice care: results from the BioCAPTURE network. *British Journal of Dermatology.* 2014;171(5):1189-1196.
105. Office for National Statistics. National life tables: England and Wales 2014-16. 2017; https://www.ons.gov.uk/releases/nationallifetablesuk2014to2016.
106. Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch Dermatol.* 2005;141(12):1537-1541.
107. Gelfand JM, Troxel AB, Lewis JD, et al. The risk of mortality in patients with psoriasis: results from a population-based study. *Archives of Dermatology.* 2007;143(12):1493-1499.
108. Pickard AS, Gooderham M, Hartz S, Nicolay C. EQ-5D health utilities: exploring ways to improve upon responsiveness in psoriasis. *J Med Econ.* 2017;20(1):19-27.
109. Kind P, Hardman G, Macran S. *UK population norms for EQ-5D, Working Papers.* Centre for Health Economics, University of York1999.
110. NHS Improvement. National Schedule of Reference Costs - Year 2016-17. https://improvement.nhs.uk/resources/reference-costs/. Accessed August 2018.
111. Personal Social Services Research Unit. *Unit Costs of Health and Social Care.* Canterbury: Personal Social Services Research Unit;2017.
112. Personal Social Services Research Unit. The hospital & community health services (HCHS) index. In: Curtis L, Burns A, eds. *Unit costs of health and social care 2016.* Canterbury: Personal Social Services Research Unit,; 2016.
113. Fonia A, Jackson K, Lereun C, Grant DM, Barker JN, Smith CH. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis. *Br J Dermatol.* 2010;163(4):807-816.
114. Egeberg A, Ottosen MB, Gniadecki R, et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. *British Journal of Dermatology.* 2018;178(2):509-519.

B.5 Appendices

The following appendices have been incorporated in a separate document that accompanies the submission.

Appendix	Title
Appendix C	Summary of product characteristics (SmPC) and European public assessment report (EPAR)
Appendix D	Identification, selection and synthesis of clinical evidence
Appendix E	Subgroup analysis
Appendix F	Adverse reactions
Appendix G	Published cost-effectiveness studies
Appendix H	Health-related quality-of-life studies
Appendix I	Cost and healthcare resource identification, measurement and valuation
Appendix J	Clinical outcomes and disaggregated results from the model
Appendix K	Checklist of confidential information
Appendix L	Additional information relative to the NMA
Appendix M	Additional clinical data from the reSURFACE studies

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Single technology appraisal

Tildrakizumab for treating moderate to severe plaque psoriasis [ID1060]

Dear Company,

The Evidence Review Group, York NHS Centre for Reviews and Dissemination and Centre for Health Economics, and the technical team at NICE have looked at the submission received on Monday 13th August 2018 from Almirall. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm on 12 September 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sharlene Ting, Technical Lead (Sharlene.Ting@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Jamie Elvidge
Technical Adviser – Technology Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

CLINICAL TRIALS

Phase IIb trial: NCT01225731

A1. PRIORITY QUESTION. Company submission (CS), section B.2.2, table 4 (pages 22-23) and section B.2.3 (pages 26-34). The company's phase IIb dose-finding study is used in the economic model. Similar to the study details provided in section B.2.3 for the phase III trials (reSURFACE1 and reSURFACE2), please provide full details of the phase IIb trial, including a schematic diagram detailing the study design and the baseline characteristics of the population.

Phase III trials: reSURFACE1 and reSURFACE2

CONSORT flow diagram

A2. PRIORITY QUESTION. Appendices, Appendix D5, Figures 4-5 (pages 34-35). The CONSORT diagrams of patient flow in Appendix D5 do not provide data for Part 3 or for long-term follow-up phases.

- For reSURFACE1 and reSURFACE2, please provide patient numbers for Part 3 and the long-term extension study for the groups randomised to tildrakizumab 100mg and tildrakizumab 200mg at the beginning of Part 1. Please provide the number of patients (with reasons, if available) who:
    - discontinued at week 28 due to non-response
    - entered Part 3 as responders
    - entered Part 3 as partial responders
    - received at least one dose of study medication in Part 3
    - entered the long-term extension study
    - did not enter the long-term extension study.
- Please clarify whether any stopping rules were applied to Part 3 and the long-term follow up phase (for example, treatment must be discontinued in non-responders), or whether patients were permitted to continue taking treatment regardless of response.

Baseline characteristics

A3. CS, section B.2.3, table 8 (pages 33-34). Table 8 provides the baseline characteristics of the populations in reSURFACE1 and reSURFACE2.

- For all groups in both trials, please provide the number of patients:
    - previously treated with more than one biological treatment
    - previously treated with a systemic non-biological treatment

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- For the data on the number of patients "previously treated with biologicals", please provide a breakdown of the biological treatment and associated number of patients.

Psoriasis Area and Severity Index (PASI) responses

A4. For reSURFACE1 and reSURFACE2, please report the Psoriasis Area and Severity Index responses (PASI 50, PASI 75, PASI 90 and PASI 100) at week 28 for the following subgroups:

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

Subgroup analyses

A5. PRIORITY QUESTION. Appendices, Appendix E, Figures 16-23 (pages 211-219). Appendix E provides the results of 4 subgroup analyses:

- previous use of biological therapy for psoriasis
- body weight (baseline weight ≤90kg and >90kg)
- previous use of phototherapy and systemic non-biological therapy (which includes fumaric acid, methotrexate, methotrexate sodium, ciclosporin, acitretin, calcium monoethyl fumarate (+) dimethyl fumarate (+) magnesium monoethyl fumarate (+) zinc monoethyl fumarate, dimethyl fumarate and apremilast
- severity of psoriasis assessed in patients with a baseline PASI <20 and ≥20.
    - For the results of all subgroup analyses, please provide the number of patients in each arm.
    - For the subgroup analyses on patients with 'previous use of biological therapy', and patients with 'previous use of phototherapy and systemic non-biological therapy', please provide results at 28 weeks.

EQ-5D-3L in reSURFACE1

A6. PRIORITY QUESTION. CS, section B.2.6.7 (page 61) and Appendices, Appendix M (pages 628-629). Section B.2.6.7 states "EQ-5D index as well as the individual component scores and change from baseline were collected at weeks 12, 28, 40, 52 and 64 (see Appendix M)." However, Appendix M does not provide any data on EQ-5D. Please provide descriptive statistics for the EQ-5D outcome including, sample sizes, missing data, follow-up time points, EQ-5D scores at baseline and follow up for each treatment, details and results of any statistical tests performed.

Dermatology Life Quality Index (DLQI)

A7. CS, section B.2.6.7 (pages 58-60). For the outcome Dermatology Life Quality Index, please provide the results of the change from baseline for Part 1 (Week 12) and Part 2

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(Week 28) of the reSURFACE1 and reSURFACE2 studies. Please report the number of patients, mean, standard deviation, 95% confidence interval and p values in a table.

Study group	Dermatology Life Quality Index score (mean, standard deviation)				
	Baseline	At 12 weeks	At 24 weeks	Change from baseline at 12 weeks (95% confidence interval, *p* value)	Change from baseline at 24 weeks (95% confidence interval, *p* value)

Adverse reactions – injection site reactions

A8. CS, section B.2.10, Table 24 (pages 80-82). The company submission states that there is a low rate of injection site reactions with tildrakizumab in the reSURFACE studies. Table 24 provides data on injection site reactions for only reSURFACE2.

- Please clarify whether there is a difference in injection site reaction rates in reSURFACE1 and reSURFACE2, given that that the blinding protocol in reSURFACE2 required biweekly injections.
- Please provide details of the injection site reaction rates for reSURFACE1.

Blinding in phase IIb and phase III trials

A9. CS, section B.2.2, tables 4-6 (pages 22-25), "CSR for reSURFACE1 [ACIC]", section 9.4.4 (page 96) and "CSR for reSURFACE2 [ACIC]", section 9.4.3.2 (page 86).

- The company submission states that all trials were 'double-blind'. Given that tildrakizumab comes in 100mg vials, please clarify how many injections are needed to administer a 200mg dose.
- Please clarify how adequate blinding is maintained in administering different doses. The clinical study reports (CSR) for reSURFACE1 and reSURFACE2 state that "[redacted]". Please provide details of the process.

NETWORK META-ANALYSIS

Comparators

A10. PRIORITY QUESTION. CS, section B.1.1, table 1 (pages 10-11), section B.2.9, "Indirect and mixed treatment comparisons" (pages 63-64) and Appendices, Appendix D.7, Table 8 (page 46). The company submission considered that apremilast, dimethyl fumarate and infliximab, all included in the NICE scope, are not relevant comparators to the decision problem. However, it included apremilast, dimethyl fumarate, risankizumab (not included in the scope) and unlicensed doses in the network meta-analysis to provide a more complete network.

- Please provide additional justification for excluding infliximab from the network meta-analysis.

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- Appendix D.7, Table 8 lists the selection criteria for the network meta-analysis. The comparators do not include risankizumab. Please clarify why risankizumab has been included the network meta-analysis.

Outcomes

A11. CS, section B.2.2, Tables 5-6 (pages 24-25) and Appendices, Appendix D.7, Table 8 (page 46). The phase III trials' co-primary endpoints included the Physician's Global Assessment. This is considered to be an important outcome in clinical practice. Appendix D.7, Table 8 does not include this outcome in the selection criteria for the network meta-analysis. Please justify why this outcome was not considered for a network meta-analysis. If available, please present the results of this outcome from the network meta-analysis.

Stage I analysis

Placebo adjustment

A12. PRIORITY QUESTION. CS, section B.2.9, "Results of stage I: sensitivity analyses – results" (page 76). The company submission states that "The impact of placebo adjustment was assessed and found not to offer any advantages over the model without placebo adjustment (details excluded)."

- Please provide full details of the results of the network meta-analysis using placebo adjustment for the Stage I analysis, including:
    - tables summarising the risk ratios, including the median and 95% credible intervals for both the fixed effects and random effects analyses for the PASI outcomes
    - tables summarising the absolute predicted PASI responses, including the median and 95% credible intervals for both the fixed effects and random effects analyses for each PASI level, that is, PASI 50, PASI 75, PASI 90 and PASI 100
    - additional justification for the above statement, including reference to goodness of fit measures (such as deviance information criterion and residual deviance)
    - a table summarising placebo response rates for the PASI outcomes for all the trials included in the network meta-analysis.
- Please provide all the files required to run all Stage I analyses and additional requested sensitivity analyses (see below) in WinBUGS, including data, model and initial values for every chain.

Sensitivity analyses

A13. PRIORITY QUESTION. CS, section B.2.9, "Results of stage I: sensitivity analyses – results" (page 76). The company submission provides 2 sensitivity analyses at stage 1: "including data from 12 weeks only" and "examining the impact of placebo adjustment".

- For the following additional sensitivity analyses:

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  - sensitivity analysis 1: excluding phase 2 trials
  - sensitivity analysis 2: excluding unlicensed doses and comparators not included in the NICE scope
  - sensitivity analysis 3: including infliximab trials

  please provide the following results, along with associated goodness of fit statistics:

  - tables summarising the risk ratios, including the median and 95% credible intervals for both the fixed effects and random effects analyses, with and without placebo adjustment, for the PASI outcomes.
  - tables summarising the absolute predicted PASI responses, including the median and 95% credible intervals for both the fixed effects and random effects analyses, with and without placebo adjustment, for each PASI level, that is, PASI 50, PASI 75, PASI 90 and PASI 100.

- Please provide all the files required to run all Stage I analyses and additional requested sensitivity analyses (see above) in WinBUGS, including data, model and initial values for every chain.

Stage III analysis – characteristics of data source

A14. PRIORITY QUESTION. CS, section B.2.9 (page 66) and Appendices, Appendix D.8, Table 14. Table 14 provides PASI data for 24 or 28 weeks, which are used in the stage III network meta-analysis. Please clarify, by adding extra columns to Table 14, whether the data are from:

- a blinded, controlled phase of the study
- an uncontrolled, blinded phase of the study
- an uncontrolled, unblinded phase of the study.

Appendix L

Appendix L.8

A15. PRIORITY QUESTION. Appendices, Appendix L.8, Tables 84-91 (pages 403-410). Tables 84 to 91 provide the results of the network meta-analysis at 24/28 weeks. Please compare these results with controlled direct comparisons at 24/28 weeks, providing a table of the trials, comparisons, available data and risk ratios from the direct comparisons.

Appendix L.12

A16 Appendices, Appendix L.12, Forest plots (pages 566-605). Appendix L.12 provides forest plots of the 'relative risk and 95% CI' for each direct placebo comparison. Please clarify whether these are the results of the network meta-analysis or of separate pairwise meta-analyses.

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Section B: Clarification on cost-effectiveness data

Comparators

B1. PRIORITY QUESTION. CS, section B.3.2, 'Intervention technology and comparators' (page 95). The company submission states that "infliximab is included in the NICE pathway for very severe psoriasis and is also not a relevant comparator and will not compete directly with tildrakizumab". It is unclear whether the company wishes to make a case for the use of tildrakizumab for this specific 'very severe' subgroup (PASI ≥20, DLQI >18) or is seeking a more restrictive positioning compared to other biological treatments that have been compared with infliximab. If the company is not seeking a more restrictive positioning, please provide an additional scenario including infliximab as a potential comparator.

Model structure

Health state

B2. CS, section B.2.9 (pages 63-66) and section B.3.2 'Model structure' (pages 90-92). The network meta-analysis in the company submission includes PASI 100 as a separate outcome. However, its economic model uses a single health state: PASI ≥90. Recent NICE technology appraisals in psoriasis (for example, TA511 and TA442) have used 2 separate states: PASI 90-99 and PASI 100. Please justify why a single state (PASI ≥90) has been used.

Cycle length

B3. CS, section B.3.2 'Model structure' (pages 91-92). The company submission states that in order to simplify the model structure, a 14-week cycle was applied. This is the midpoint of induction periods for other treatments (12 or 16 weeks). Please justify why a shorter cycle length was not used; for example, a 2-week cycle length would have allowed the induction periods of other comparators to precisely match the stopping rules in existing NICE recommendations.

Stopping rule

B4. PRIORITY QUESTION. CS, section B.2.6.4, 'Appropriate timepoint to assess treatment response' (page 51), section B3.3 (pages 98-101) and section B.3.8.4, 'Scenario 5: alternative efficacy data for all comparators (28 weeks)' (page 142). The company submission states that "it would be biologically implausible, evidently premature, and clinically burdensome to specialists and patients, to implement an assessment and stopping rule at week 12. Therefore, Almirall proposes an assessment time point at 28 weeks". However, its economic model includes an induction period of 14 weeks, at which point treatment response is assessed.

- Please justify the assumption of a 14 week stopping rule for tildrakizumab in the base-case analysis.

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- The company presents a scenario analysis that increased the induction period from 14 to 28 weeks for all treatments.
    - Please present an additional scenario that assumes a 28 week stopping rule for tildrakizumab only.
    - Please include an additional function in the Excel model to allow flexibility to select either a 14 or 28 week induction period for tildrakizumab and a separate function to select either a 14 or 28 week induction period for the comparators.

Quality of life

Regression methods

B5. CS, section B.3.4, 'Health-related quality-of-life data used in the cost-effectiveness analysis' (pages 105-106). The company submission used health state utilities based on EQ-5D data at week 12 from reSURFACE1.

- Please provide details of the regression methods used to estimate change in EQ-5D from baseline to 12 weeks.
- Please confirm whether any adjustments were made for baseline EQ-5D and/or other covariates.

European valuation set

B6. PRIORITY QUESTION. CS, section B.3.4, 'Health-related quality-of-life data from clinical trials' (page 103). The company submission states that "index utility estimates were calculated based on the EQ-5D data collected in the reSURFACE study using the European valuation set".

- Please revise the EQ-5D analyses using index utility estimates based on the UK value set (Dolan 1997) rather than the European value set.
- Please provide the following additional analyses using the UK value set:
    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 >10 subgroup)
    c) results for a) and b) adjusting for baseline-EQ-5D score.

Costs

'Non-responder' costs

B7. CS, section B.3.5 (pages 106-110). The company submission does not include 'non-responder' costs. Please present a scenario analysis incorporating additional costs for 'non-responders' in line with other NICE technology appraisal guidance on psoriasis (for example, TA475 and TA442).

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Best supportive care costs

B8. CS, section B.3.5 (page 109). In the base-case analysis, the company uses best supportive care costs based on values adopted in the cost-effectiveness model developed for the NICE clinical guideline on psoriasis (CG153). NICE technology appraisal guidance on psoriasis (for example, TA419 and TA350) recognise the uncertainty and shortcomings of existing sources for resource use for best supportive care but concluded that estimates were likely to be closer to Fonia *et al.* than to the estimates from NICE CG153. As a result, estimates from Fonia *et al.* have been used in all subsequent appraisals (for example TA442, TA475, TA511 and TA521). Please provide further justification for estimating best supportive care costs using NICE CG153 rather than Fonia *et al.*

Probabilistic Sensitivity Analyses

B9. PRIORITY QUESTION. CS, section B.3.8 (page 119). The probabilistic sensitivity analysis inputs for PASI outcomes are based on independent distributions, which ignore the correlations between PASI categories and between individual treatments from the network meta-analyses. Please revise the probabilistic sensitivity analysis ensuring that the PASI outcomes are directly informed by the WinBUGS CODA.

Excel model – Programming error

B10. PRIORITY QUESTION. The percent change calculation used in the model and applied to the population norm age is calculated incorrectly – see details and example below. Please revise and resubmit the Excel model correcting for this error.

Error details:

The submitted model calculates the percent change as:

- Percent change = (V2 – V1)/V2 X 100
- Where V2 = mean PASI score from regression model
- V1 = Population norm utility at baseline age

The correct formula should be:

- Percent change = (V2 – V1)/V1 X 100

Example:

- Formula cell F4 on the Population utility norms sheet = (Utility!AB16-'Population Utility Norms'!$D$4)/Utility!AB16 or (0.67 – 0.871)/0.67 = -30%. Applying this to the start age (46) population utility of 0.871 gives a result of 0.6097 (example: cell I35). However, the calculated utility should equal the mean PASI score from the model when applied to the start age population utility. When using the correct formula, the correct percentage reduction is (0.67 – 0.871)/0.871 = -23.08%. Applying this to the start age population utility of 0.871 = 0.67.

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Section C: Textual clarifications and additional points

C1. CS, section B.3.2, Figure 23 (page 92). Please clarify whether the PASI 75-90 and PASI >90 states should refer to PASI 75-89 and PASI ≥90.

C2. CS, section B.2.9, Table 21 (page 67-69) and Appendices, Appendix D.7, Table 9 (pages 47-52).

- The labelling of the trials in Table 21 in the company submission is not consistent with that in Table 9 in Appendix D. Please amend Table 21 and add the main reference details to Table 21 to make it easier to identify the trials correctly.
- The risankizumab *vs* ustekinumab study labelled "Papp 2017" in Table 9 in Appendix D does not appear in other tables. Please clarify.

Almirall response to clarification questions – 12th September 2018

Single Technology Appraisal

Tildrakizumab for treating moderate to severe plaque psoriasis [ID1060]

Thank you for the opportunity to provide additional information and clarification on the clinical and cost effectiveness data for tildrakizumab for the treatment of moderate to severe plaque psoriasis. Please note that in responding to the clarification questions, we have provided as much information as possible and appreciate that, due to the data requested, the response document is quite lengthy.

We have listed the references applicable to each response after that response and indicated those references that were not cited in or provided with our original submission document. We have included a zipped file with additional references, text files and Excel spreads that relate to our responses. Details of these additional files are included in a table at the end of this document

Section A: Clarification on effectiveness data

CLINICAL TRIALS

Phase IIb trial: NCT01225731

A1. PRIORITY QUESTION. Company submission (CS), section B.2.2, table 4 (pages 22-23) and section B.2.3 (pages 26-34). The company's phase IIb dose-finding study is used in the economic model. Similar to the study details provided in section B.2.3 for the phase III trials (reSURFACE1 and reSURFACE2), please provide full details of the phase IIb trial, including a schematic diagram detailing the study design and the baseline characteristics of the population.

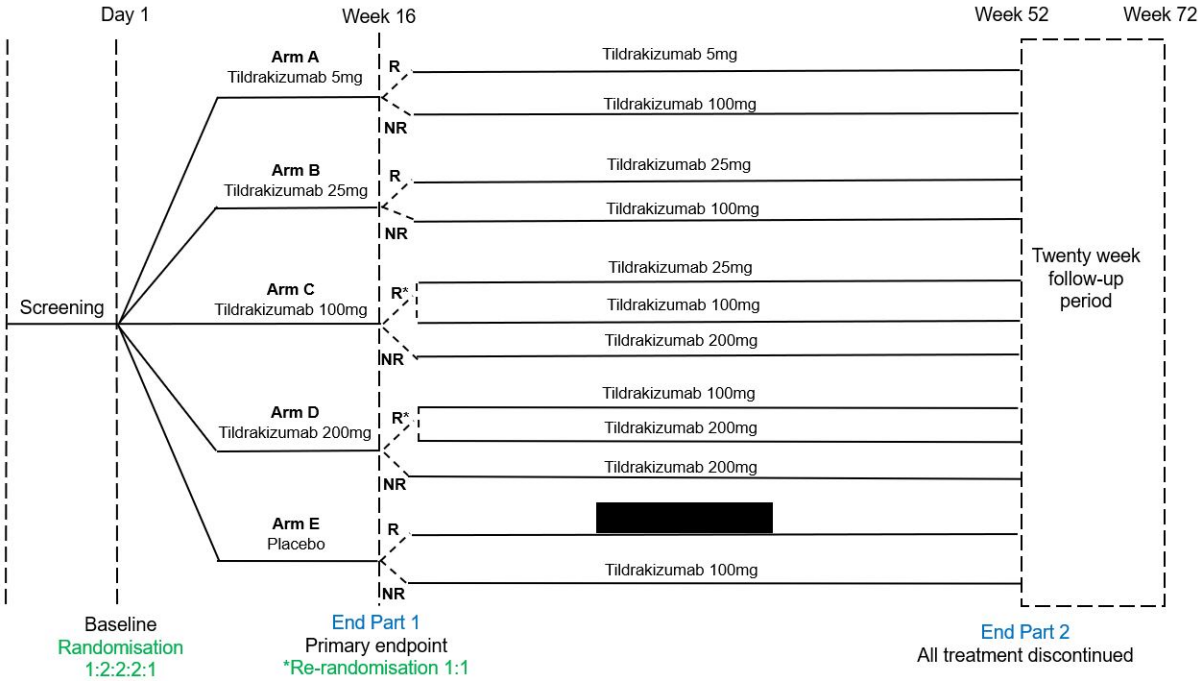
Response:

Summary of methodology of the Phase IIb dose finding study of tildrakizumab (NCT01225731)

Trial design

Figure 1 illustrates the study design for the Phase IIb dose finding study of tildrakizumab. The details of treatment assignment for each part of the study are included in Table 1, along with a full summary of the trial methodology.

Figure 1: Phase IIb dose finding study of tildrakizumab: trial design



In Part 1 subjects received tildrakizumab or placebo at Week 0 and Week 4. In Part 2 all subjects received active treatment every 12 weeks. 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.

Summary of trial methodology

Table 1: Summary of trial methodology for the Phase IIb dose finding study of tildrakizumab

Location	64 sites in the USA, Canada, Japan and Europe.
Trial design	Phase IIb randomised, double-blind, parallel group, dose-finding study. Randomised subjects (N=355) were stratified by baseline weight (≤90kg, >90kg) and prior exposure to biological therapy for psoriasis (yes / no).
Eligibility criteria for subjects	Eligible subjects: • Aged ≥18 years old, of either gender. • Had predominantly plaque psoriasis for longer than six months, defined as a Psoriasis Area and Severity Index (PASI) score ≥12; psoriasis body surface area involvement ≥10%; and a Physician Global Assessment (PGA) of moderate, marked or severe at baseline. • Candidates for phototherapy or systemic therapy. Major exclusion criteria included latent or active tuberculosis; prior exposure to two or more TNF-α antagonists with discontinuation owing to lack of efficacy; and uncontrolled arrhythmias, cardiac revascularisation, stroke and uncontrolled hypertension or diabetes within six months of screening.
Trial design	Subjects received tildrakizumab subcutaneously (sc) at the dose level and frequency described below. To maintain blinding, a matching tildrakizumab placebo was provided and administered by sc injection. **Part 1: Weeks 0 to 16** Subjects were randomly assigned (1:2:2:2:1) to receive tildrakizumab or placebo as follows: • **Arm A (N=42)**: Tildrakizumab 5mg at baseline (Week 0) and Week 4. • **Arm B (N=92)**: Tildrakizumab 25mg at baseline (Week 0) and Week 4. • **Arm C (N=89)**: Tildrakizumab 100mg at baseline (Week 0) and Week 4. • **Arm D (N=86)**: Tildrakizumab 200mg at baseline (Week 0) and Week 4. • **Arm E (N=46)**: Placebo at baseline (Week 0) and Week 4. **Part 2: Weeks 16 to 52** Treatment allocation was based on responder status. Responders were subjects who achieved ≥75% improvement in PASI response from baseline and non-responders were subjects who achieved <50% improvement in PASI response from baseline. • **Arm A**: Responders received tildrakizumab 5mg every 12 weeks; non-responders received tildrakizumab 100mg every 12 weeks. • **Arm B**: Responders received tildrakizumab 25mg every 12 weeks; non-responders received tildrakizumab 100mg every 12 weeks.

	• **Arm C**: Responders were re-randomised at Week 16 (1:1) to receive tildrakizumab 25mg or tildrakizumab 100mg every 12 weeks; non-responders receiving tildrakizumab 200mg every 12 weeks.. • **Arm D**: Responders were re-randomised at Week 16 (1:1) to receive tildrakizumab 100mg or tildrakizumab 200mg every 12 weeks; non-responders receiving tildrakizumab 200mg every 12 weeks.. • **Arm E**: Responders received tildrakizumab 25mg every 12 weeks; non-responders received tildrakizumab 100mg every 12 weeks. Subjects discontinued treatment at Week 52 and entered a twenty-week follow-up period (Part III, Weeks 52 to 72).
Permitted and disallowed concomitant medication	**Medications prohibited prior to randomisation** [redacted] **Medications prohibited during the trial after randomisation** [redacted] **Medications allowed during the trial** [redacted]

	• [redacted]
Primary, secondary and safety endpoints	The primary analysis (Part I) was performed on the full analysis set (FAS) (i.e. all randomised subjects who received one or more doses of treatment and had baseline and one or more post-baseline efficacy measurements in Part I). **Primary efficacy endpoint:** The proportion of subjects with a reduction in PASI score of at least 75% from baseline at Week 16. **Secondary endpoints (Part I):** 1. PASI 75 response at Week 12. 2. Proportion of subjects with a PGA status of 'cleared' or 'minimal' at Week 16. 3. Proportion of subjects achieving a ≥90% reduction in PASI score (PASI 90) at Week 16. 4. Time to PASI 75. 5. Mean change from baseline in the Dermatology Life Quality Index (DLQI) at Week 16. **Secondary endpoints (Part II):** 1. PASI 75 response at Week 52 (grouped by PASI status at Week 16). 2. Proportion of subjects with a PGA status of 'cleared' or 'minimal' at Week 52. **During Part III**, relapse was assessed as the time that Week 52 improvement from baseline was reduced by >50% (in subjects who attained PASI 75 at Week 52). **Safety assessment** Safety was evaluated by continuous monitoring of adverse events and periodic assessment of clinical safety, electrocardiograms and vital signs.
Pre-planned subgroups	[redacted]

Abbreviations: BSA: body surface area; DLQI: Dermatology Life Quality Index; FAS: full analysis set; kg: kilograms; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; sc: subcutaneously; USA: United States of America; UV: ultraviolet. Source: Papp et al 2015 and Phase IIb dose finding study clinical study report (CSR).

Statistical analysis in the Phase IIb dose finding study of tildrakizumab

Table 2 includes details of the sample size and power calculations, statistical analysis, and data management for subjects who withdrew from the Phase IIb dose finding study of tildrakizumab.

Table 2: Statistical analysis conducted in the Phase IIb dose finding study of tildrakizumab

Hypothesis / objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
To evaluate the safety and efficacy of subcutaneous tildrakizumab in patients with moderate-to-severe chronic plaque psoriasis.	The primary end point was analysed using the Cochran–Mantel-Haenszel test stratified by baseline weight (≤90kg, >90kg) and prior exposure to biological therapy for psoriasis (yes / no). For multiplicity control, each tildrakizumab dose was compared with placebo sequentially (200mg, then 100mg, then 25mg, then 5mg). In Part II, the Week 52 PASI 75 response rates in Week 16 PASI 75 responders were summarised with 95% confidence intervals (CIs). The re-randomised 100mg and 200mg tildrakizumab groups were compared using a Chi-squared test. For the safety analysis of Part I, p values and 95% CIs were given for comparisons between each tildrakizumab dose and placebo for specified adverse events; the 95% CI for between-group differences from placebo was also given for adverse events that occurred in four or more subjects in any treatment group. No inferential testing was performed in Parts II and III.	Approximately 280 subjects were to be randomised (35 per arm for the tildrakizumab 5mg and placebo groups and 70 per arm for the tildrakizumab 25mg, 100mg and 200mg groups) to allow for 240 evaluable subjects in the FAS population for Part I (assuming a 15% dropout rate). However, due to rapid enrolment, 355 subjects were actually randomised. A 40% difference in PASI 75 response rate between tildrakizumab and placebo was estimated to give ≥90% power at a 5% level of significance (two-sided test) assuming a conservative placebo response rate of about 10% (based on previous studies). The 40% effect size was the minimal effect size considered to be clinically meaningful. The study also had ≥90% power to detect a 55% difference in PGA statuses of 'cleared' or 'minimal' between the tildrakizumab and placebo arms (5% significance level, two-sided test) for a 5% placebo response.	The last non-missing post-baseline PASI value obtained in Parts I and II was carried forward for any subject who missed the end point assessment and who had not discontinued treatment owing to lack of efficacy, loss of response, or had used prohibited medications in the corresponding part of the study. Subjects who discontinued prior to Week 16 due to lack of efficacy, loss of response, or use of prohibited medication were considered not to have achieved PASI 75; those with a missing PASI score at Week 16 were analysed by carrying over the last post-baseline non-missing PASI score.

Abbreviations: CI: confidence interval; FAS: full analysis set; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment. Source: Papp et al 2015.

Baseline characteristics of subjects across treatment groups

Demographic variables, baseline clinical characteristics, cardiovascular risk factors and prior exposure to biological therapies are summarised in Table 3 by treatment in the all subjects as randomised (ASR) populations.

Table 3: Baseline characteristics of subjects in the Phase IIb dose finding study of tildrakizumab

	Tildrakizumab 5mg (N=42)	**Tildrakizumab 25mg (N=92)**	**Tildrakizumab 100mg (N=89)**	**Tildrakizumab 200mg (N=86)**	**Placebo (N=46)**
Age (years), mean ± SD	43.2 ± 12.9	46.3 ± 13.7	45.5 ± 12.8	43.2 ± 12.6	45.9 ± 11.7
Male gender	31 (74)	60 (65)	76 (85)	65 (76)	38 (83)
Ethnicity					
White	31 (74)	78 (85)	73 (82)	73 (85)	35 (76)
Non-white	11 (26)	14 (15)	16 (18)	13 (15)	11 (24)
Hispanic / Latino	0	2 (2)	2 (2)	1 (1)	0
BMI (kg / m^2), mean ± SD	28.9 ± 5.6	28.5 ± 6.2	29.0 ± 6.0	28.5 ± 5.8	29.5 ± 6.4
Normal (<25)	12 (29)	29 (32)	21 (24)	20 (23)	10 (22)
Overweight (25 to 30)	11 (26)	32 (35)	41 (46)	38 (44)	19 (41)
Obese (≥30)	19 (45)	31 (34)	27 (30)	27 (31)	17 (37)
Prior exposure to biologic therapy (PEBT)	10 (24)	19 (21)	15 (17)	19 (22)	13 (28)
≤90kg, PEBT: Yes	5 (12)	15 (16)	13 (15)	11 (13)	7 (15)
≤90kg, PEBT: No	21 (50)	43 (47)	44 (49)	42 (49)	21 (46)
>90kg, PEBT: Yes	6 (14)	11 (12)	10 (11)	11 (13)	6 (13)
>90kg, PEBT: No	10 (24)	23 (25)	22 (25)	22 (26)	12 (26)
Previous use of TNF inhibitor therapy	9 (21)	17 (18)	15 (17)	15 (17)	12 (26)
CVD risk factors and history of CVD					
Myocardial infarction	1 (2)	0	0	1 (1)	0
Ischaemic heart disease / CAD	1 (2)	1 (1)	2 (2)	3 (3)	1 (2)
Ischaemic stroke	0	0	0	0	0
TIA	0	0	0	0	1 (2)

Peripheral vascular disease	0	1 (1)	2 (2)	0	0
Diabetes mellitus	2 (5)	10 (11)	8 (9)	5 (6)	1 (2)
Hyperlipidaemia	1 (2)	8 (9)	8 (9)	6 (7)	7 (15)
Hypertension	6 (14)	27 (29)	27 (30)	25 (29)	11 (24)
Any history of CVD	1 (2)	1 (1)	4 (4)	3 (3)	1 (2)
Family history of early CAD	0	1 (1)	0	0	0
Smoking					
Current smoker	15 (36)	25 (27)	22 (25)	22 (26)	12 (26)
Never smoked	23 (55)	54 (59)	59 (66)	57 (66)	29 (63)
Past smoker	4 (10)	13 (14)	8 (9)	7 (8)	5 (11)
Systolic BP (mmHg), mean ± SD	125.8 ± 15.0	125.1 ± 14.4	128.7 ± 15.1	127.3 ± 15.6	126.8 ± 14.3
Diastolic BP (mmHg), mean ± SD	77.9 ± 9.3	79.5 ± 9.9	80.4 ± 9.7	79.3 ± 9.5	82.2 ± 9.1
HDL-C (mmol / L), mean ± SD	1.27 ± 0.42	1.28 ± 0.33	1.31 ± 0.37	1.31 ± 0.33	1.35 ± 0.33
LDL-C (mmol / L), mean ± SD	2.98 ± 0.86	3.07 ± 0.91	3.01 ± 0.88	3.05 ± 0.96	3.29 ± 0.98
Other medical history at baseline					
Basal cell cancer	0	0	0	0	1 (2)
Psoriatic arthritis	8 (19)	15 (16)	15 (17)	15 (17)	11 (24)
Cervical cancer in situ	0	1 (1)	0	0	0

Data are n (%) in the ASR populations unless otherwise stated. Abbreviations: ASR: All subjects randomised; BMI: body mass index; BP: blood pressure; CAD: coronary artery disease; CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; kg: kilograms; LDL-C: low-density lipoprotein cholesterol; mmHg: millimetres of mercury; mmol / L: millimole per litre; PEBT: previous exposure to biologic therapy; SD: standard deviation; TIA: transient ischaemic attack; TNF: tumour necrosis factor. *Discrepancy in total PEBT and PEBT (yes) by weight is due to errors in stratification of some subjects during randomisation. Source: Papp et al 2015.

References for Question A1:

- Papp K, Thaçi D, Reich K, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. Br J Dermatol. 2015;173(4):930-939. (Provided in original submission reference pack)
- Clinical Study Report for SCH 900222/MK-3222: Randomized, double-blinded, placebo-controlled, parallel-design, dose-range finding study of subcutaneous tildrakizumab (SCH 900222/MK-3222) in subjects with moderate-to-severe chronic plaque psoriasis (protocol no. P05495) (*Academic in Confidence*) February 2017. (Provided with this response)

Phase III trials: reSURFACE1 and reSURFACE2

CONSORT flow diagram

A2. PRIORITY QUESTION. Appendices, Appendix D5, Figures 4-5 (pages 34-35). The CONSORT diagrams of patient flow in Appendix D5 do not provide data for Part 3 or for long-term follow-up phases.

- For reSURFACE1 and reSURFACE2, please provide patient numbers for Part 3 and the long-term extension study for the groups randomised to tildrakizumab 100mg and tildrakizumab 200mg at the beginning of Part 1. Please provide the number of patients (with reasons, if available) who:
    - discontinued at week 28 due to non-response
    - entered Part 3 as responders
    - entered Part 3 as partial responders
    - received at least one dose of study medication in Part 3
    - entered the long-term extension study
    - did not enter the long-term extension study.
- Please clarify whether any stopping rules were applied to Part 3 and the long-term follow up phase (for example, treatment must be discontinued in non-responders), or whether patients were permitted to continue taking treatment regardless of response.

Response:

Table 4 below shows the patient numbers for Part 3 and the long-term extension phase of reSURFACE 1 and 2. The subsequent text describes the application of stopping rules.

Table 4: patient numbers in Part 3 and the long-term extension phases of reSURFACE 1 and 2

	reSURFACE 1		reSURFACE 2	
	Tildrakizumab 100mg in Part 1	**Tildrakizumab 200mg in Part 1**	**Tildrakizumab 100mg in Part 1**	**Tildrakizumab 200mg in Part 1**
Patients in population Part 2 (all randomised subjects)[1]	**299**	**298**	**294**	**300**
-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]
Patient 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	194	192	[redacted]	[redacted]
Did not enter the long-term extension study	[redacted]	[redacted]	[redacted]	[redacted]

Sources: [1] Table 14.1.1-4 (Disposition of Subjects, Part 2), CSR from reSURFACE 1, p. 381; Table 14.1-4 (Disposition of Subjects, Part 2), CSR from reSURFACE 2, p. 343

Stopping rule between Part 2 and Part 3

In the reSURFACE 1 and reSURFACE 2 studies, stopping rules were only applied at Week 28 (between Part 2 and Part 3): subjects that had PASI <50% (non-responders, NR) from baseline, were not allowed to enter Part 3, thus discontinued.

Sources: Protocol for reSURFACE 1: 7.4.1.1 Treatment Administered: Base Study p. 50; 7.3 Trial Population p.40; Protocol for reSURFACE 2: 7.4.1.1 Treatment Administered-Base Study p. 54; 7.3 Trial Population p.42.

Stopping rule between Part 3 and long-term extension study

For reSURFACE 1 (from study protocol)

Eligible subjects for the extension study included those who had completed Part 3 of the study and achieved at least 50% improvement in PASI from baseline with tildrakizumab treatment at the end of the study (Part 3). Subjects must have received active tildrakizumab treatment within 12 weeks prior to the end of the treatment period. As such, subjects who were withdrawn from active treatment at Week 28 and did not relapse or reinitiate treatment by Week 64 (the last treatment visit), were not eligible to participate in the long-term extension study.

For reSURFACE 2 (from study protocol)

Subjects who completed the study and achieved at least 50% improvement in PASI from baseline at the end of Part 3 were eligible to participate in the extension study.

Sources: Protocol for reSURFACE 1: 2.1 Trial Design Diagram p. 9; 7.3 Trial Population p.40; Protocol reSURFACE 2: 2.1 Trial Design Diagram p. 10; 7.3 Trial Population p.38.

References for Question A2:

- Protocol for the reSURFACE 1 study (MK-3222-010, Pn010) (*Academic in Confidence*) (Provided with this response)
- Protocol for the reSURFACE 2 study (MK-3222-011, Pn011) (*Academic in Confidence*) (Provided with this response)

Baseline characteristics

A3. CS, section B.2.3, table 8 (pages 33-34). Table 8 provides the baseline characteristics of the populations in reSURFACE1 and reSURFACE2.

- For all groups in both trials, please provide the number of patients:
    - previously treated with more than one biological treatment
    - previously treated with a systemic non-biological treatment
- For the data on the number of patients “previously treated with biologicals”, please provide a breakdown of the biological treatment and associated number of patients.

Response:

Subjects previously treated with one or more biologic therapy

It is not possible to provide details of the number of subjects in the reSURFACE 1 and 2 studies who were treated with more than one biological treatment as this information was not collected during the studies.

However, it is possible to provide details of the number of subjects who were previously exposed to biologic therapy and the biologic therapies that were taken by subjects in each study.

reSURFACE 1

Table 5 provides details of the number and proportion of subjects who received biologic therapy in each treatment group in Part 1 of the RESURFACE 1 study.

Table 6 provides details of the individual biologic therapies taken in these subjects.

Table 5: Prior exposure to biologic therapy for psoriasis in Part 1 of the RESURFACE 1 study

	Tildrakizumab 100mg N=309	Tildrakizumab 200mg N=308	Placebo N=154	Total N=771
Previous exposure to biologic therapy for psoriasis, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Data are observed cases in the full analysis set in Part 1 of the reSURFACE 1 study. Source: Almirall, data on file.

Table 6: Individual biologic therapies taken by subjects who reported previously taking biologic therapies in Part 1 of the RESURFACE 1 study

	Tildrakizumab 100mg N=71	Tildrakizumab 200mg N=71	Placebo N=34	Total N=176
Individual biologic therapy, n (%)				
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]
Alefacept	[redacted]	[redacted]	[redacted]	[redacted]
Briakinumab	[redacted]	[redacted]	[redacted]	[redacted]
Efalizumab	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]

Data are observed cases in the full analysis set in Part 1 of the reSURFACE 1 study. Individual biologic therapy may have been taken by the subject for any indication it is licensed for. Source: Almirall, data on file.

reSURFACE 2

Table 7 provides details of the number and proportion of subjects who received biologic therapy in each treatment group in Part 1 of the RESURFACE 2 study. Table 8 provides details of the individual biologic therapies taken in these subjects.

Table 7: Prior exposure to biologic therapy for psoriasis in Part 1 of the RESURFACE 2 study

	Tildrakizumab 100mg N=307	Tildrakizumab 200mg N=314	Placebo N=156	Etanercept 50mg N=313	Total N=1090
Previous exposure to biologic therapy for psoriasis, n (%)					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data are observed cases in the full analysis set in Part 1 of the reSURFACE 2 study. Source: Almirall, data on file.

Table 8: Individual biologic therapies taken by subjects who reported previously taking biologic therapies in Part 1 of the RESURFACE 2 study

	Tildrakizumab 100mg N=39	Tildrakizumab 200mg N=38	Placebo N=20	Etanercept 50mg N=37	Total N=134
Individual biologic therapy, n (%)					
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alefacept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Briakinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data are observed cases in the full analysis set in Part 1 of the reSURFACE 2 study. Individual biologic therapy may have been taken by the subject for any indication it is licensed for. Source: Almirall, data on file.

Patients previously treated with systemic non-biologic therapy

reSURFACE 1

Table 9 provides details of the number and proportion of subjects who were previously treated with a systemic non-biologic therapy in Part 1 of the RESURFACE 1 study.

Table 9: Prior treatment with a systemic non-biologic therapy in Part 1 of the RESURFACE 1 study

	Tildrakizumab 100mg N=309	Tildrakizumab 200mg N=308	Placebo N=154	Total N=771
Previous treatment with a systemic non-biologic therapy, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Data are observed cases in the full analysis set in Part 1 of the reSURFACE 1 study. Previous systemic non-biologic therapy may have been taken by the subject for any indication it is licensed for. Source: Almirall, data on file.

reSURFACE 2

Table 10 provides details of the number and proportion of subjects who were previously treated with a systemic non-biologic therapy in Part 1 of the RESURFACE 2 study.

Table 10: Prior treatment with a systemic non-biologic therapy in Part 1 of the RESURFACE 2 study

	Tildrakizumab 100mg N=307	Tildrakizumab 200mg N=314	Placebo N=156	Etanercept 50mg N=313	Total N=1090
Previous treatment with a systemic non-biologic therapy, n (%)					
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data are observed cases in the full analysis set in Part 1 of the reSURFACE 2 study. Previous systemic non-biologic therapy may have been taken by the subject for any indication it is licensed for. Source: Almirall, data on file.

Reference for Question A3:

- Almirall data on file: Subjects previously treated with biologic therapy and subjects receiving systemic non-biologic therapy. (*Academic in Confidence*) (Provided with this response)

PASI responses

A4. For reSURFACE1 and reSURFACE2, please report the Psoriasis Area and Severity Index responses (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.

Response:

The tables below provide PASI responses at Week 28 for subjects in reSURFACE 1 (MK-3222-10) and reSURFACE 2 (MK-3222-11) who had PASI <50; PASI ≥50 and <75; and PASI ≥75 at week 12. Table 11 to Table 13 present observed (OC) data for reSURFACE 1, reSURFACE 2 and pooled reSURFACE 1 and 2 data, respectively. Table 14 to Table 16 present non-responder imputation for missing data (NR) for reSURFACE 1, reSURFACE 2 and pooled reSURFACE 1 and 2 data, respectively.

In the tables, MK-3222-10 refers to data from reSURFACE 1 and MK-3222-11 refers to data from reSURFACE 2. The following dosage information also applies

- 0/100 = Placebo in Part 1 and tildrakizumab 100mg in Part 2
- 0/200 = Placebo in Part 1 and tildrakizumab 200mg in Part 2
- 100/100 = Tildrakizumab 100mg in Part 1 and tildrakizumab 100mg in Part 2
- 200/200 = Tildrakizumab 200mg in Part 1 and tildrakizumab 200mg in Part 2

Table 11 Proportion of Subjects with PASI50, PASI75, PASI90, and PASI100 Response at week 28 (Missing=OC). Descriptive statistics by PASI at week 12 group (< 50, >=50 and < 75, >= 75). Full Analysis Set Part 2 (MK-3222-10, reSURFACE 1)

PASI 50 at week 12	Parameter at week 28	0/100 (N=74) n (%)	0/200 (N=72) n (%)	100/100 (N=299) n (%)	200/200 (N=298) n (%)	Total (N=743) n (%)
< 50						
>= 50 and < 75						
>= 75						
>= 50 and < 75						
>= 75						
Missing						

Source: CSR for reSURFACE 1.

Table 12 Proportion of Subjects with PASI50, PASI75, PASI90, and PASI100 Response at week 28 (Missing=OC).
Descriptive statistics by PASI at week 12 group (< 50, >=50 and < 75, >= 75).
Full Analysis Set Part 2 (MK-3222-11, reSURFACE 2)

PASI 50 at week 12	Parameter at week 28	0/100 (N=69) n (%)	0/200 (N=72) n (%)	100/100 (N=294) n (%)	200/200 (N=299) n (%)	50/ 50 (N=289) n (%)	Total (N=1023) n (%)
< 50							
>= 50 and < 75							
>= 75							
>= 75							
Missing							

Source: CSR for reSURFACE 2.

Table 13 Proportion of Subjects with PASI50, PASI75, PASI90, and PASI100 Response at week 28 (Missing=OC).
Descriptive statistics by PASI at week 12 group (< 50, >=50 and < 75, >= 75).
Full Analysis Set Part 2 (MK-3222-10/11, Pooled data from reSURFACE 1 and reSURFACE 2)

PASI 50 at week 12	Parameter at week 28	0/100 (N=143) n (%)	0/200 (N=144) n (%)	100/100 (N=593) n (%)	200/200 (N=597) n (%)	50/ 50 (N=289) n (%)	Total (N=1766) n (%)
< 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 50 and < 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CSRs for reSURFACE 1 and reSURFACE 2.

Table 14 Proportion of Subjects with PASI50, PASI75, PASI90, and PASI100 Response at week 28 (Missing=NR). Descriptive statistics by PASI at week 12 group (< 50, >=50 and < 75, >= 75). Full Analysis Set Part 2 (MK-3222-10, reSURFACE 1).

PASI 50 at week 12	Parameter at week 28	0/100 (N=74) n (%)	0/200 (N=72) n (%)	100/100 (N=299) n (%)	200/200 (N=298) n (%)	Total (N=743) n (%)
< 50						
>= 50 and < 75						
>= 75						
>= 75						
Missing						

Source: CSR for reSURFACE 1.

Table 15 Proportion of Subjects with PASI50, PASI75, PASI90, and PASI100 Response at week 28 (Missing=NR). Descriptive statistics by PASI at week 12 group (< 50, >=50 and < 75, >= 75). Full Analysis Set Part 2 (MK-3222-11, reSURFACE 2).

PASI 50 at week 12	Parameter at week 28	0/100 (N=69) n (%)	0/200 (N=72) n (%)	100/100 (N=294) n (%)	200/200 (N=299) n (%)	50/ 50 (N=289) n (%)	Total (N=1023) n (%)
< 50							
>= 50 and < 75							
>= 75							
>= 75							
Missing							

Source: CSR for reSURFACE 2.

Table 16 Proportion of Subjects with PASI50, PASI75, PASI90, and PASI100 Response at week 28 (Missing=NR).
Descriptive statistics by PASI at week 12 group (< 50, >=50 and < 75, >= 75).
Full Analysis Set Part 2 (MK-3222-10/11, Pooled data from reSURFACE 1 and reSURFACE 2).

PASI 50 at week 12	Parameter at week 28	0/100 (N=143) n (%)	0/200 (N=144) n (%)	100/100 (N=593) n (%)	200/200 (N=597) n (%)	50/ 50 (N=289) n (%)	Total (N=1766) n (%)
< 50							
>= 50 and < 75							
>= 75							
>= 75							
Missing							

Source: CSRs for reSURFACE 1 and reSURFACE 2.

References for Question A4

- Clinical study report for MK-3222 P010 (reSURFACE 1): A 64-week, phase 3, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (*Academic in Confidence*). 13 February 2017. (Provided in original submission reference pack).
- Clinical study report for MK-3222 P011 (reSURFACE 2): A 52-week, phase 3, randomized, active comparator and placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (*Academic in Confidence*). 22 February 2017. (Provided in original submission reference pack).

Subgroup analyses

A5. PRIORITY QUESTION. Appendices, Appendix E, Figures 16-23 (pages 211-219). Appendix E provides the results of 4 subgroup analyses:

- previous use of biological therapy for psoriasis
- body weight (baseline weight ≤90kg and >90kg)
- previous use of phototherapy and systemic non-biological therapy (which includes fumaric acid, methotrexate, methotrexate sodium, ciclosporin, acitretin, calcium monoethyl fumarate (+) dimethyl fumarate (+) magnesium monoethyl fumarate (+) zinc monoethyl fumarate, dimethyl fumarate and apremilast
- severity of psoriasis assessed in patients with a baseline PASI <20 and ≥20.
    - For the results of all subgroup analyses, please provide the number of patients in each arm.
    - For the subgroup analyses on patients with 'previous use of biological therapy', and patients with 'previous use of phototherapy and systemic non-biological therapy', please provide results at 28 weeks.

Response:

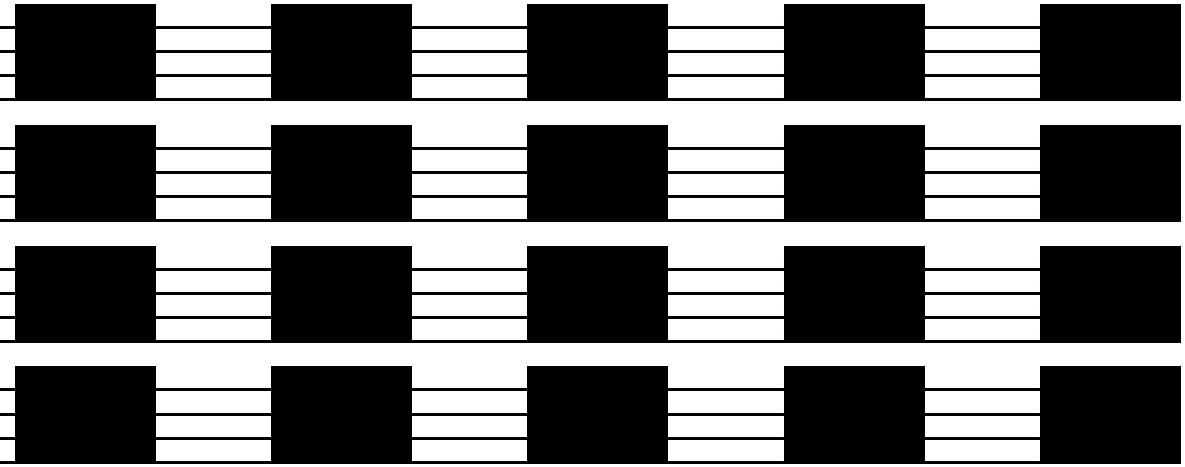
Table 17 to Table 28 provide data on the patient numbers in each arm of the subgroup analyses which were used in the Forest plots (Figures 16 to 23 in Appendix E). The pooled data are provided followed by separate data for reSURFACE 1 and 2 studies.

Table 29 to Table 40 provide the results for PASI 75, PASI 90, PASI 100 and PGA responses at Week 28. As before, pooled data are provided followed by data for the individual reSURFACE studies.

In the tables, MK-3222-10 refers to data from reSURFACE 1 and MK-3222-11 refers to data from reSURFACE 2.

Table 17 **Figure 1/5.1. Forest plot for PASI 75 at Week 12 by subgroups.**
Full Analysis Set Part 1 (MK-3222-10/11 Pooled data from reSURFACE 1 and reSURFACE 2).

Group		PASI 75	Placebo (N=310)	MK-3222 100mg (N=616)	MK-3222 200mg (N=622)	Etanercept 50mg (N=313)	Total (N=1861)
1	No	No					
		Yes					
	Yes	No					
		Yes					
2	<=90	No					
		Yes					
	>90	No					
		Yes					
3	No	No					
		Yes					
	Yes	No					
		Yes					
4	<20	No					
		Yes					
	>=20	No					
		Yes					



Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSRs for reSURFACE 1 and reSURFACE 2.

Table 18 **Figure 1/5.2. Forest plot for PASI 75 at Week 12 by subgroups. Full Analysis Set Part 1 (MK-3222-10, reSURFACE 1).**

Group		PASI 75	Placebo (N=154)	MK-3222 100mg (N=309)	MK-3222 200mg (N=308)	Total (N=771)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]
		Yes				
	Yes	No				
		Yes				
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]
		Yes				
	>90	No				
		Yes				
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]
		Yes				
	Yes	No				
		Yes				
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]
		Yes				
	>=20	No				
		Yes				

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 1.

Table 19 **Figure 1/5.3. Forest plot for PASI 75 at Week 12 by subgroups.**
Full Analysis Set Part 1 (MK-3222-11, reSURFACE 2).

Group		PASI 75	Placebo (N=156)	MK-3222 100mg (N=307)	MK-3222 200mg (N=314)	Etanercept 50mg (N=313)	Total (N=1090)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	Yes	No					
		Yes					
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	>90	No					
		Yes					
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	Yes	No					
		Yes					
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	>=20	No					
		Yes					

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 2.

Table 20 **Figure 2/6.1. Forest plot for PASI 90 at Week 12 by subgroups.**
Full Analysis Set Part 1 (MK-3222-10/11 Pooled data from reSURFACE 1 and reSURFACE 2).

Group		PASI 90	Placebo (N=310)	MK-3222 100mg (N=616)	MK-3222 200mg (N=622)	Etanercept 50mg (N=313)	Total (N=1861)
1	No	No					
		Yes					
	Yes	No					
		Yes					
2	<=90	No					
		Yes					
	>90	No					
		Yes					
3	No	No					
		Yes					
	Yes	No					
		Yes					
4	<20	No					
		Yes					
	>=20	No					
		Yes					

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSRs for reSURFACE 1 and reSURFACE 2.

Table 21 **Figure 2/6.2. Forest plot for PASI 90 at Week 12 by subgroups. Full Analysis Set Part 1 (MK-3222-10, reSURFACE 1).**

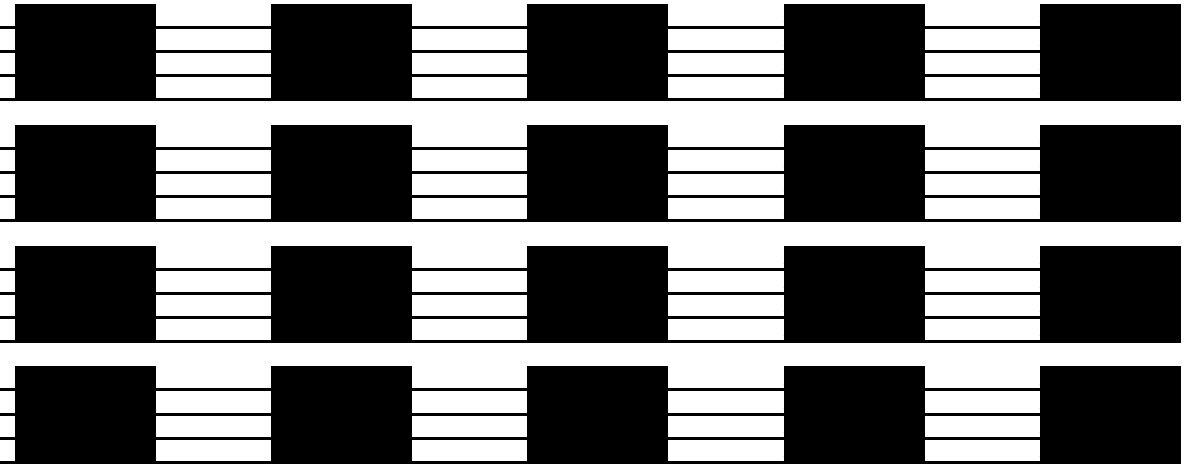
Group		PASI 90	Placebo (N=154)	MK-3222 100mg (N=309)	MK-3222 200mg (N=308)	Total (N=771)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]
		Yes				
	Yes	No				
		Yes				
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]
		Yes				
	>90	No				
		Yes				
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]
		Yes				
	Yes	No				
		Yes				
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]
		Yes				
	>=20	No				
		Yes				

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 1.

Table 22 **Figure 2/6.3. Forest plot for PASI 90 at Week 12 by subgroups. Full Analysis Set Part 1 (MK-3222-11, reSURFACE 2).**

Group		PASI 90	Placebo (N=156)	MK-3222 100mg (N=307)	MK-3222 200mg (N=314)	Etanercept 50mg (N=313)	Total (N=1090)
1	No	No					
		Yes					
	Yes	No					
		Yes					
2	<=90	No					
		Yes					
	>90	No					
		Yes					
3	No	No					
		Yes					
	Yes	No					
		Yes					
4	<20	No					
		Yes					
	>=20	No					
		Yes					



Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 2.

Table 23 **Figure 3/7.1. Forest plot for PASI 100 at Week 12 by subgroups.**
Full Analysis Set Part 1 (MK-3222-10/11 Pooled data from reSURFACE 1 and reSURFACE 2).

Group		PASI 100	Placebo (N=310)	MK-3222 100mg (N=616)	MK-3222 200mg (N=622)	Etanercept 50mg (N=313)	Total (N=1861)
1	No	No					
		Yes					
	Yes	No					
		Yes					
2	<=90	No					
		Yes					
	>90	No					
		Yes					
3	No	No					
		Yes					
	Yes	No					
		Yes					
4	<20	No					
		Yes					
	>=20	No					
		Yes					

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSRs for reSURFACE 1 and reSURFACE 2.

Table 24 **Figure 3/7.2. Forest plot for PASI 100 at Week 12 by subgroups.**
Full Analysis Set Part 1 (MK-3222-10, reSURFACE 1).

Group		PASI 100	Placebo (N=154)	MK-3222 100mg (N=309)	MK-3222 200mg (N=308)	Total (N=771)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]
		Yes				
	Yes	No				
		Yes				
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]
		Yes				
	>90	No				
		Yes				
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]
		Yes				
	Yes	No				
		Yes				
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]
		Yes				
	>=20	No				
		Yes				

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 1.

Table 25 **Figure 3/7.3. Forest plot for PASI 100 at Week 12 by subgroups.**
Full Analysis Set Part 1 (MK-3222-11, reSURFACE 2).

Group		PASI 100	Placebo (N=156)	MK-3222 100mg (N=307)	MK-3222 200mg (N=314)	Etanercept 50mg (N=313)	Total (N=1090)
1	No	No					
		Yes					
	Yes	No					
		Yes					
2	<=90	No					
		Yes					
	>90	No					
		Yes					
3	No	No					
		Yes					
	Yes	No					
		Yes					
4	<20	No					
		Yes					
	>=20	No					
		Yes					

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 2.

Table 26 **Figure 4/8.1. Forest plot for PGA (0/1) at Week 12 by subgroups.**
Full Analysis Set Part 1 (MK-3222-10/11 Pooled data from reSURFACE 1 and reSURFACE 2).

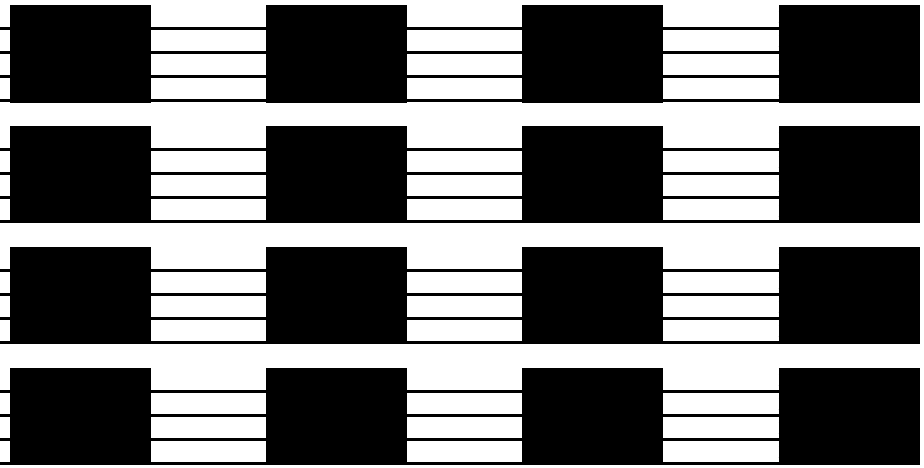
Group		PGA (0/1)	Placebo (N=310)	MK-3222 100mg (N=616)	MK-3222 200mg (N=622)	Etanercept 50mg (N=313)	Total (N=1861)
1	No	No					
		Yes					
	Yes	No					
		Yes					
2	<=90	No					
		Yes					
	>90	No					
		Yes					
3	No	No					
		Yes					
	Yes	No					
		Yes					
4	<20	No					
		Yes					
	>=20	No					
		Yes					

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSRs for reSURFACE 1 and reSURFACE 2.

Table 27 **Figure 4/8.2. Forest plot for PGA (0/1) at Week 12 by subgroups. Full Analysis Set Part 1 (MK-3222-10, reSURFACE 1).**

Group		PGA (0/1)	Placebo (N=154)	MK-3222 100mg (N=309)	MK-3222 200mg (N=308)	Total (N=771)
1	No	No				
		Yes				
	Yes	No				
		Yes				
2	<=90	No				
		Yes				
	>90	No				
		Yes				
3	No	No				
		Yes				
	Yes	No				
		Yes				
4	<20	No				
		Yes				
	>=20	No				
		Yes				



Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 1.

Table 28 **Figure 4/8.3. Forest plot for PGA (0/1) at Week 12 by subgroups. Full Analysis Set Part 1 (MK-3222-11, reSURFACE 2).**

Group		PGA (0/1)	Placebo (N=156)	MK-3222 100mg (N=307)	MK-3222 200mg (N=314)	Etanercept 50mg (N=313)	Total (N=1090)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	Yes	No					
		Yes					
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	>90	No					
		Yes					
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	Yes	No					
		Yes					
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	>=20	No					
		Yes					

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 2.

Table 29 Descriptive statistics for PASI 75 at Week 28 by subgroups.
Full Analysis Set Part 2 (MK-3222-10/11 Pooled data from reSURFACE 1 and reSURFACE 2).

Group		PASI 75	0/100 (N=143)	0/200 (N=144)	100/100 (N=593)	200/200 (N=597)	50/ 50 (N=289)	Total (N=1766)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>90	No						
		Yes						
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>=20	No						
		Yes						

Notes: **Group 1 = Previous use of biological therapy**
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSRs for reSURFACE 1 and reSURFACE 2.

Table 30 Descriptive statistics for PASI 75 at Week 28 by subgroups.
Full Analysis Set Part 2 (MK-3222-10, reSURFACE 1).

Group		PASI 75	0/100 (N=74)	0/200 (N=72)	100/100 (N=299)	200/200 (N=298)	Total (N=743)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	Yes	No					
		Yes					
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	>90	No					
		Yes					
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	Yes	No					
		Yes					
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	>=20	No					
		Yes					

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 1.

Table 31 Descriptive statistics for PASI 75 at Week 28 by subgroups.
Full Analysis Set Part 2 (MK-3222-11, reSURFACE 2).

Group		PASI 75	0/100 (N=69)	0/200 (N=72)	100/100 (N=294)	200/200 (N=299)	50/ 50 (N=289)	Total (N=1023)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>90	No						
		Yes						
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>=20	No						
		Yes						

Notes: **Group 1 = Previous use of biological therapy**
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 2.

Table 32 Descriptive statistics for PASI 90 at Week 28 by subgroups.
Full Analysis Set Part 2 (MK-3222-10/11 Pooled data from reSURFACE 1 and reSURFACE 2).

Group		PASI 90	0/100 (N=143)	0/200 (N=144)	100/100 (N=593)	200/200 (N=597)	50/ 50 (N=289)	Total (N=1766)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>90	No						
		Yes						
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>=20	No						
		Yes						

Notes: **Group 1 = Previous use of biological therapy**
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSRs for reSURFACE 1 and reSURFACE 2.

Table 33 Descriptive statistics for PASI 90 at Week 28 by subgroups.
Full Analysis Set Part 2 (MK-3222-10, reSURFACE 1).

Group		PASI 90	0/100 (N=74)	0/200 (N=72)	100/100 (N=299)	200/200 (N=298)	Total (N=743)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	Yes	No					
		Yes					
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	>90	No					
		Yes					
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	Yes	No					
		Yes					
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	>=20	No					
		Yes					

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 1.

Table 34 Descriptive statistics for PASI 90 at Week 28 by subgroups.
Full Analysis Set Part 2 (MK-3222-11, reSURFACE 2).

Group		PASI 90	0/100 (N=69)	0/200 (N=72)	100/100 (N=294)	200/200 (N=299)	50/ 50 (N=289)	Total (N=1023)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>90	No						
		Yes						
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>=20	No						
		Yes						

Notes: **Group 1 = Previous use of biological therapy**
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 2.

Table 35 Descriptive statistics for PASI 100 at Week 28 by subgroups.
Full Analysis Set Part 2 (MK-3222-10/11 Pooled data from reSURFACE 1 and reSURFACE 2).

Group		PASI 100	0/100 (N=143)	0/200 (N=144)	100/100 (N=593)	200/200 (N=597)	50/ 50 (N=289)	Total (N=1766)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>90	No						
		Yes						
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>=20	No						
		Yes						

Notes: **Group 1 = Previous use of biological therapy**
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSRs for reSURFACE 1 and reSURFACE 2.

Table 36 Descriptive statistics for PASI 100 at Week 28 by subgroups.
Full Analysis Set Part 2 (MK-3222-10, reSURFACE 1).

Group		PASI 100	0/100 (N=74)	0/200 (N=72)	100/100 (N=299)	200/200 (N=298)	Total (N=743)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	Yes	No					
		Yes					
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	>90	No					
		Yes					
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	Yes	No					
		Yes					
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	>=20	No					
		Yes					

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 1.

Table 37 Descriptive statistics for PASI 100 at Week 28 by subgroups.
Full Analysis Set Part 2 (MK-3222-11, reSURFACE 2).

Group		PASI 100	0/100 (N=69)	0/200 (N=72)	100/100 (N=294)	200/200 (N=299)	50/ 50 (N=289)	Total (N=1023)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>90	No						
		Yes						
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>=20	No						
		Yes						

Notes: **Group 1 = Previous use of biological therapy**
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 2.

Table 38 Descriptive statistics for PGA (0/1) at Week 28 by subgroups.
Full Analysis Set Part 2 (MK-3222-10/11 Pooled data from reSURFACE 1 and reSURFACE 2).

Group		PGA (0/1)	0/100 (N=143)	0/200 (N=144)	100/100 (N=593)	200/200 (N=597)	50/ 50 (N=289)	Total (N=1766)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>90	No						
		Yes						
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>=20	No						
		Yes						

Notes: **Group 1 = Previous use of biological therapy**
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSRs for reSURFACE 1 and reSURFACE 2.

Table 39 Descriptive statistics for PGA (0/1) at Week 28 by subgroups.
Full Analysis Set Part 2 (MK-3222-10, reSURFACE 1).

Group		PGA (0/1)	0/100 (N=74)	0/200 (N=72)	100/100 (N=299)	200/200 (N=298)	Total (N=743)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	Yes	No					
		Yes					
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	>90	No					
		Yes					
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	Yes	No					
		Yes					
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes					
	>=20	No					
		Yes					

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 1.

Table 40 Descriptive statistics for PGA (0/1) at Week 28 by subgroups.
Full Analysis Set Part 2 (MK-3222-11, reSURFACE 2).

Group		PGA (0/1)	0/100 (N=69)	0/200 (N=72)	100/100 (N=294)	200/200 (N=299)	50/ 50 (N=289)	Total (N=1023)
1	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
2	<=90	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>90	No						
		Yes						
3	No	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	Yes	No						
		Yes						
4	<20	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Yes						
	>=20	No						
		Yes						

Notes: Group 1 = Previous use of biological therapy
Group 2 = Weight group
Group 3 = Previous use of phototherapy and systemic non-biological therapy
Group 4 = Baseline PASI

Source: CSR for reSURFACE 2.

References for Question A4

- Clinical study report for MK-3222 P010 (reSURFACE 1): A 64-week, phase 3, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (*Academic in Confidence*). 13 February 2017. (Provided in original submission reference pack).
- Clinical study report for MK-3222 P011 (reSURFACE 2): A 52-week, phase 3, randomized, active comparator and placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (*Academic in Confidence*). 22 February 2017. (Provided in original submission reference pack).

EQ-5D-3L in reSURFACE1

A6. PRIORITY QUESTION. CS, section B.2.6.7 (page 61) and Appendices, Appendix M (pages 628-629). Section B.2.6.7 states "EQ-5D index as well as the individual component scores and change from baseline were collected at weeks 12, 28, 40, 52 and 64 (see Appendix M)." However, Appendix M does not provide any data on EQ-5D. Please provide descriptive statistics for the EQ-5D outcome including, sample sizes, missing data, follow-up time points, EQ-5D scores at baseline and follow up for each treatment, details and results of any statistical tests performed.

Response:

Data collection

In reSURFACE 1, EQ-5D data were collected at Weeks 12, 28, 52 and 64. (Note that Week 40 was listed in the CSR in error; data were not collected at this time point.) Included in the CSR are summary tables of the EQ-5D index score over time and change from baseline in Parts 1 and 2 (Week 0 to Week 28) and Part 3 (Weeks 28 to Week 64) of reSURFACE 1; together with tables summarising EQ-5D individual component scores (mobility, self-care, usual activities, pain / discomfort, and anxiety / depression) over time and change from baseline over the same time periods.

Results:

Week 0 to Week 28

- In the tildrakizumab 100mg and tildrakizumab 200mg groups, EQ-5D scores remained consistent and similar over Part 1 and Part 2 of the study (Weeks 12 and 28) (Company submission B.2.6 page 61).
- In subjects randomised to placebo in Part 1 and re-randomised to tildrakizumab 100mg or tildrakizumab 200mg in Part 2, EQ-5D scores at Week 28 were similar to those observed in the other treatment sequence groups.

Week 28 to Week 64

- In all treatment sequence groups (i.e. subjects randomised to tildrakizumab 100mg or 200mg in Part 1 who were PASI 75 responders or partial responders at Week 28 and subjects randomised to placebo in Part 1 and re-randomised to tildrakizumab in Part 2), EQ-5D index scores and change from baseline during Part 3 (Week 28 to Week 64) remained consistent over time with no notable differences observed between the treatment sequence groups.

Tabulated data

- Table 41 shows the summary of EQ-5D index scores over time for Parts 1 and 2 of reSURFACE 1 (i.e. Weeks 0 to 28).
- Table 42 to Table 43 show the summary of EQ-5D index score over time for Part 3 of reSURFACE 1 (i.e. Weeks 28 to 64).
- If additional detail is required please refer to the CSR (Section 11.3.6 page 243-4 and Tables 14.2.1-40 to 14.2.1-47 pages 869 to 891) which provides details of the index scores and also individual component scores over time for Parts 1, 2 and 3 of reSURFACE 1.

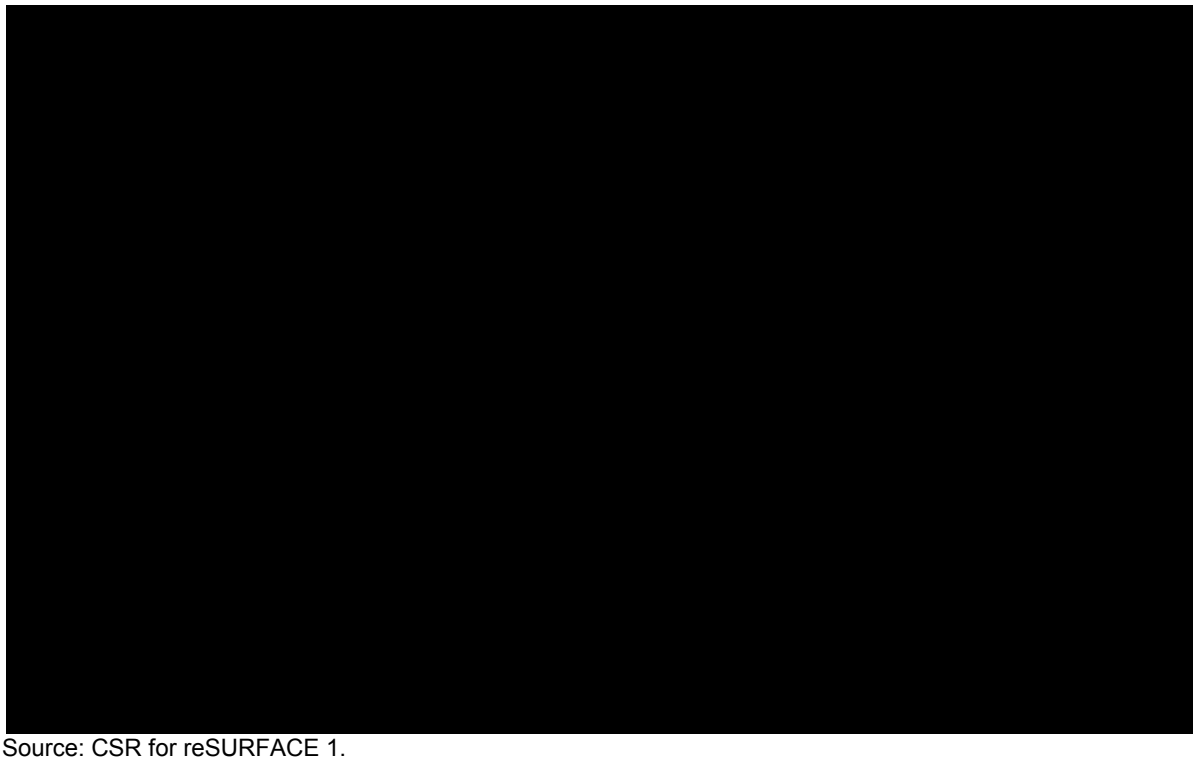
Statistical analyses

- As EQ-5D was an exploratory end-point, no statistical tests were applied to the data, so no p-values or inferences are displayed in Table 41 to Table 43.
- A paired T-test was performed between baseline and Week 28, baseline and Week 64 and Week 28 and Week 64 in Part 3 treatment arms. As the difference observed in each domain did not appear to be significant, only the total score for the EQ-5D was analysed. The results are shown in Table 44 to Table 46.

Reference for Question A6:

- Clinical study report for MK-3222 P010 (reSURFACE 1): A 64-week, phase 3, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (*Academic in Confidence*). 13 February 2017. (Provided in original submission reference pack)

Table 41: Summary of EQ-5D index score over time: Parts 1 and 2



Source: CSR for reSURFACE 1.

Table 42: Summary of EQ-5D index score over time: Part 3

Source: CSR for reSURFACE 1

Table 43: Summary of EQ-5D Index Score Over Time: Part 3

Source: CSR for reSURFACE 1

Table 44: Paired T-Test EQ-5D baseline to Week 28

EQ-5D					
Treatment Arm	**N**	**Baseline**	**Week 28**	**Change**	**p-value**
100/100/R0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100/100/R100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100/100/PR100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100/100/PR200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
200/200/R0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
200/200/R200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
200/200/PR200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0/100/R100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0/100/PR100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0/200/R200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0/200/PR200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PR, partial responder; R, responder; W, week; 100: tildrakizumab 100mg; 200: tildrakizumab 200mg; 0: placebo. Source: CSR for reSURFACE 1.

Table 45: Paired T-Test EQ-5D baseline to Week 64

EQ-5D					
Treatment Arm	**N**	**Baseline**	**Week 64**	**Change**	**p-value**
100/100/R0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100/100/R100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100/100/PR100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100/100/PR200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
200/200/R0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
200/200/R200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
200/200/PR200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0/100/R100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0/100/PR100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0/200/R200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0/200/PR200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PR, partial responder; R, responder; W, week; 100: tildrakizumab 100mg; 200: tildrakizumab 200mg; 0: placebo. Source: CSR for reSURFACE 1.

Table 46: Paired T-test EQ-5D Week 28 to Week 64

EQ-5D					
Treatment Arm	**N**	**Week 28**	**Week 64**	**Change**	**p-value**
100/100/R0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100/100/R100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100/100/PR100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100/100/PR200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
200/200/R0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
200/200/R200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
200/200/PR200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0/100/R100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0/100/PR100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0/200/R200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0/200/PR200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PR, partial responder; R, responder; W, week; 100: tildrakizumab 100mg; 200: tildrakizumab 200mg; 0: placebo. Source: CSR for reSURFACE 1.

Reference for Question A6

- Clinical study report for MK-3222 P010 (reSURFACE 1): A 64-week, phase 3, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (*Academic in Confidence*). 13 February 2017. (Provided in original submission reference pack).

Dermatology Life Quality Index (DLQI)

A7. CS, section B.2.6.7 (pages 58-60). For the outcome Dermatology Life Quality Index, please provide the results of the change from baseline for Part 1 (Week 12) and Part 2 (Week 28) of the reSURFACE1 and reSURFACE2 studies. Please report the number of patients, mean, standard deviation, 95% confidence interval and p values in a table.

Study group	**Dermatology Life Quality Index score (mean, standard deviation)**				
	Baseline	**At 12 weeks**	**At 24 weeks**	**Change from baseline at 12 weeks (95% confidence interval, *p* value)**	**Change from baseline at 24 weeks (95% confidence interval, *p* value)**

NOTE the company confirmed with the ERG (during the clarification teleconference on 31.8.18) that the data required were for Week 28 (rather than Week 24).

Response:

The data below represent the change from baseline in Dermatology Life Quality Index (DLQI) over time using a constrained longitudinal analysis. These analyses are adjusted by prior biologic (Yes / No) and the weight (≤90kg, >90kg), according to the study protocols. The analyses only take into account those subjects from the full analysis population (FAS) who have information regarding weight and prior biologic therapy. Since it was only possible to generate a p value for the comparison of tildrakizumab versus placebo at Week 12 in the reSURFACE 1 study, only results comparing baseline with Week 12 data are presented. For the reSURFACE 2 study, it is possible to present results for both Weeks 12 and Week 28 as a statistical comparison was conducted for tildrakizumab verses placebo at Week 12 and tildrakizumab versus etanercept at Week 28.

reSURFACE 1 Study

Table 47 shows the change from baseline in the DLQI over time (to Week 12) using the constrained longitudinal analysis in the FAS population in the reSURFACE 1 study.

The change from baseline in DLQI score at Week 12 was significantly greater in the tildrakizumab 100mg and 200mg groups compared with the placebo group (p<0.001 for each comparison).

Table 47: Constrained longitudinal data analysis of change from baseline in DLQI at Week 12 in reSURFACE 1

Treatment	N	Baseline Mean (SD)	Week 12 Mean (SD)	Change from baseline	
				Mean (SD)	Least Square Mean (95% CI)†
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tildrakizumab 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tildrakizumab 200mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise comparison				**Difference in Least Square Mean (95% CI)**	**P value**
Tildrakizumab 100mg versus placebo				[redacted]	[redacted]
Tildrakizumab 200mg versus placebo				[redacted]	[redacted]
Root Mean Squares error of change = [redacted]					

†Based on a constrained longitudinal data analysis model including terms for time, the interaction of time by treatment, body weight (≤90 kg, >90 kg), and prior exposure to biologic therapy for psoriasis (Yes / No). N = Number of randomised subjects who received at least one dose of study medication and with baseline and post-baseline values in Part 1 of the reSURFACE 1 study. Baseline means only include subjects who have baseline and Week 12 values. Abbreviations: CI: confidence interval; SD: standard deviation. Source: CSR for reSURFACE 1 (Table 11-21).

reSURFACE 2 Study

Table 48 shows the change from baseline in the DLQI over time (Week 12) using the constrained longitudinal analysis in the FAS population in the reSURFACE 1 study.

The change from baseline in DLQI score at Week 12 was greater in the tildrakizumab 100mg and 200 mg groups compared with the placebo group (nominal p<0.001 for each comparison) and the etanercept group (nominal p=0.002 and p=0.001, respectively).

Table 48: Constrained longitudinal data analysis of change from baseline in DLQI at Week 12 in reSURFACE 2

Treatment	N	Baseline Mean (SD)	Week 12 Mean (SD)	Change from baseline	
				Mean (SD)	Least Square Mean (95% CI)†
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tildrakizumab 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tildrakizumab 200mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pairwise comparison	Difference in Least Square Mean (95% CI)	P value
Tildrakizumab 100mg versus placebo	[redacted]	[redacted]
Tildrakizumab 200mg versus placebo	[redacted]	[redacted]
Tildrakizumab 100mg versus etanercept	[redacted]	[redacted]
Tildrakizumab 200mg versus etanercept	[redacted]	[redacted]
Root Mean Squares error of change = [redacted]		

†Based on a constrained longitudinal data analysis model including terms for time, the interaction of time by treatment, body weight (≤90 kg, >90 kg), and prior exposure to biologic therapy for psoriasis (Yes / No). N = Number of randomised subjects who received at least one dose of study medication and with baseline and post-baseline values in Part 1 of the reSURFACE 2 study. Baseline means only include subjects who have baseline and Week 12 values. Abbreviations: CI: confidence interval; SD: standard deviation. Source: CSR for reSURFACE 2 (Table 11-27).

An analysis of change from baseline in DLQI at Week 28 in subjects randomised to tildrakizumab 100mg, tildrakizumab 200mg, or etanercept in Part 1 of the reSURFACE 2 study using the constrained longitudinal analysis model in the FAS population is presented in Table 49.

The proportions of subjects with DLQI score of 0 or 1 at Week 28 were greater in the tildrakizumab 100mg and 200mg groups compared with the etanercept group (nominal p<0.001 for each comparison).

Table 49: Constrained longitudinal data analysis of change from baseline in DLQI at Week 28 in reSURFACE 2

Treatment	N	Baseline Mean (SD)	Week 28 Mean (SD)	Change from baseline	
				Mean (SD)	Least Square Mean (95% CI)†
Tildrakizumab 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tildrakizumab 200mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise comparison				Difference in Least Square Mean (95% CI)	P value
Tildrakizumab 100mg versus etanercept				[redacted]	[redacted]
Tildrakizumab 200mg versus etanercept				[redacted]	[redacted]
Root Mean Squares error of change = [redacted]					

†Based on a constrained longitudinal data analysis model including terms for time, the interaction of time by treatment, body weight (≤90 kg, >90 kg), and prior exposure to biologic therapy for psoriasis (Yes / No). N = Number of randomised subjects who received at least one dose of study medication and with baseline and post-baseline values in Part 1 and Part 2 of the reSURFACE 2 study. Baseline means only include subjects who have baseline and Week 28 values. Abbreviations: CI: confidence interval; SD: standard deviation. Source: CSR for reSURFACE 2 (Table 11-29).

References for Question A7

- Clinical study report for MK-3222 P010 (reSURFACE 1): A 64-week, phase 3, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (*Academic in Confidence*). 13 February 2017. (Provided in original submission reference pack).
- Clinical study report for MK-3222 P011 (reSURFACE 2): A 52-week, phase 3, randomized, active comparator and placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (*Academic in Confidence*). 22 February 2017. (Provided in original submission reference pack).

Adverse reactions – injection site reactions

A8. CS, section B.2.10, Table 24 (pages 80-82). The company submission states that there is a low rate of injection site reactions with tildrakizumab in the reSURFACE studies. Table 50 provides data on injection site reactions for only reSURFACE2.

- Please clarify whether there is a difference in injection site reaction rates in reSURFACE1 and reSURFACE2, given that that the blinding protocol in reSURFACE2 required biweekly injections.
- Please provide details of the injection site reaction rates for reSURFACE1.

Response:

- Due to the low number of reported events it is not possible to draw robust comparisons of the injection site reaction rates between the two studies.
- Table 50 below shows reports of injection site reactions from reSURFACE 1 for Parts 1, 2 and 3 of the study. If additional detail is required please refer to the CSR (Section 12.2.2.2 page 313; Tables 14.3.1-11 page 1211; 14.3.1-12 page 1222; Section 12.2.2.4 page 315; Table 14.3.1-18 page 1263), which was included as part of the reference pack provided with the submission.

Table 50: Injection site reactions for reSURFACE 1

	Part 1			Part 2		Part 3	
	Placebo N=154	Tildrakizumab 100mg N=309	Tildrakizumab 200mg N=308	Tildrakizumab 100mg N=374	Tildrakizumab 200mg N=370	Tildrakizumab 100mg N=316	Tildrakizumab 200mg N=370
Injection site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sources: Table 14.3.1-11; Table 14.3.1-12; Table 14.3.1-18 of the reSURFACE 1 CSR.

Reference for Question A8

- Clinical study report for MK-3222 P010 (reSURFACE 1): A 64-week, phase 3, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (*Academic in Confidence*). 13 February 2017. (Provided in original submission reference pack).

Blinding in phase IIb and phase III trials

A9. CS, section B.2.2, tables 4-6 (pages 22-25), "CSR for reSURFACE1 [ACIC]", section 9.4.4 (page 96) and "CSR for reSURFACE2 [ACIC]", section 9.4.3.2 (page 86).

- The company submission states that all trials were 'double-blind'. Given that tildrakizumab comes in 100mg vials, please clarify how many injections are needed to administer a 200mg dose.
- Please clarify how adequate blinding is maintained in administering different doses. The clinical study reports (CSR) for reSURFACE1 and reSURFACE2 state that "All subjects underwent administration of additional placebo doses to maintain blinding". Please provide details of the process.

Response:

Administration of a 200mg dose of tildrakizumab

- To administer a 200mg dose, two injections, each of 100mg, are administered.

Blinding in the reSURFACE studies

A double-blind technique was used. Investigators, participants, and study personnel were blinded to group allocation (study medication assignment) and remained blinded until completion of the base study (to Week 64 in reSURFACE 1 and Week 52 in reSURFACE 2). Blinding to treatment assignment was maintained at all investigational sites.

During the studies (up to Week 64 in reSURFACE 1 and Week 52 in reSURFACE 2) all subjects were administered additional placebo doses (tildrakizumab or etanercept) to maintain blinding according to the details in the study protocols as outlined in the clinical study reports. During the extension studies after the base studies had been unblinded, study treatments were administered in an open-label manner.

Tildrakizumab and its matching placebo were identical in appearance, packaged identically and administered in exactly the same way (by subcutaneous injection via pre-filled syringes) so that treatment blinding was maintained. In the reSURFACE 2 study, the matching etanercept placebo was identical in appearance, packaged identically and administered in exactly the same way (by subcutaneous injection) as etanercept. During the blinded portion of the trials, subjects were allocated blinded kits that contained a sufficient number of pre-filled syringes to maintain the dosing schedule. During the open-label extension phase of the study, subjects received tildrakizumab in either a pre-filled syringe or auto-injector format for the duration of the trial.

References for Question A8

- Clinical study report for MK-3222 P010 (reSURFACE 1): A 64-week, phase 3, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (*Academic in Confidence*). 13 February 2017. (Provided in original submission reference pack).
- Clinical study report for MK-3222 P011 (reSURFACE 2): A 52-week, phase 3, randomized, active comparator and placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (*Academic in Confidence*). 22 February 2017. (Provided in original submission reference pack).

NETWORK META-ANALYSIS

Comparators

A10. PRIORITY QUESTION. CS, section B.1.1, table 1 (pages 10-11), section B.2.9, "Indirect and mixed treatment comparisons" (pages 63-64) and Appendices, Appendix D.7, Table 8 (page 46). The company submission considered that apremilast, dimethyl fumarate and infliximab, all included in the NICE scope, are not relevant comparators to the decision problem. However, it included apremilast, dimethyl fumarate, risankizumab (not included in the scope) and unlicensed doses in the network meta-analysis to provide a more complete network.

- Please provide additional justification for excluding infliximab from the network meta-analysis.
- Appendix D.7, Table 8 lists the selection criteria for the network meta-analysis. The comparators do not include risankizumab. Please clarify why risankizumab has been included the network meta-analysis.

Response:

Exclusion of infliximab from the network meta-analysis

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).

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. However, following receipt of the ERG clarification questions, and for transparency, an analysis with infliximab has been presented in response to question B1.

Inclusion of risankizumab in the network meta-analysis

Risankizumab is 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.

Outcomes

A11. CS, section B.2.2, Tables 5-6 (pages 24-25) and Appendices, Appendix D.7, Table 8 (page 46). The phase III trials' co-primary endpoints included the Physician's Global Assessment. This is considered to be an important outcome in clinical practice. Appendix D.7, Table 8 does not include this outcome in the selection criteria for the network meta-analysis. Please justify why this outcome was not considered for a network meta-analysis. If available, please present the results of this outcome from the network meta-analysis.

Response:

The network meta-analysis (NMA) to support the Almirall submission was developed to inform the health economic model via probability of achieving a specific PASI response. PASI response is the most relevant efficacy parameter in the population of moderate to severe psoriasis patients and is consistently reported across clinical studies and is also relevant to clinical practice. Based on this, PGA data were not included as an outcome in the selection criteria for the NMA and these data were not extracted from included studies. 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) (Robinson et al, 2012) and the perspective expressed in the same publication that PASI is better validated and more detailed as a measure of efficacy.

References for Question A11.

- Robinson A, Kardos M, Kimball AB**.** Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): Why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. *J Am Acad Dermatol.* 2012;66(3):369-375. (Provided with this response)

Stage I analysis

Placebo adjustment

A12. PRIORITY QUESTION. CS, section B.2.9, "Results of stage I: sensitivity analyses – results" (page 76). The company submission states that "The impact of placebo adjustment was assessed and found not to offer any advantages over the model without placebo adjustment (details excluded)."

- Please provide full details of the results of the network meta-analysis using placebo adjustment for the Stage I analysis, including:
    - tables summarising the risk ratios, including the median and 95% credible intervals for both the fixed effects and random effects analyses for the PASI outcomes
    - tables summarising the absolute predicted PASI responses, including the median and 95% credible intervals for both the fixed effects and random effects analyses for each PASI level, that is, PASI 50, PASI 75, PASI 90 and PASI 100
    - additional justification for the above statement, including reference to goodness of fit measures (such as deviance information criterion and residual deviance)
    - a table summarising placebo response rates for the PASI outcomes for all the trials included in the network meta-analysis.

- Please provide all the files required to run all Stage I analyses and additional requested sensitivity analyses (see below) in WinBUGS, including data, model and initial values for every chain.

Response:

Placebo adjustment analysis

The placebo adjustment is a technique to account for additional variation in placebo responses. Both fixed effect and random effects models have been considered. Regarding model fit, the random effects models fared much better, with a difference of deviance information criterion (DIC) values of 30 (see Table 51).

Table 51: Measures of model fit, with/without placebo adjustment

	Fixed effect, **no** placebo adjustment	Fixed effect, placebo adjustment	Random effects, **no** placebo adjustment	Random effects, placebo adjustment
DIC				
pD				
Deviance = DIC - pD				

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.

There is substantial heterogeneity for placebo treatment effects present in the selected studies.

Table 52: Placebo responses within network, Weeks 12 to 16

	PASI 50	PASI 75	PASI 90	PASI 100
Meta-analysis, fixed effects				
Meta-analysis, random effects				
I^2				
Minimum				
Maximum				
Number of studies reporting this value				

Abbreviations: I^2: I squared statistic; PASI: Psoriasis Area and Severity Index.

The observed heterogeneity could be cited as justification for choosing to use placebo adjustment in spite of the higher DIC. However, within the network there are fewer studies reporting on PASI 50 Placebo than on other PASI levels for placebo: 26 studies report on PASI 50, 41 studies report on PASI 75, 37 studies report on PASI 90, and 29 studies report on PASI 100. Higher PASI levels are less heterogeneous and play a more important role within the network. Therefore, the benefit of placebo adjustment for this particular network is unclear.

The supporting results and WINBUGs code are provided in accompanying file: **Additional references and files / Text files and excel spreadsheets / A12**. Table 53 shows which files relate to which questions.

Table 53: Data requested and related files

Data Requested	**Filenames where the results and code can be located within additional file A12**
Tables summarising the risk ratios, including the median and 95% credible intervals for both the fixed effect and random effects analyses for the PASI outcomes	Fixed effect tables: PlaceboAdjFixed2.xlsx Random effects tables: PlaceboAdjRandom2.xlsx
Tables summarising the absolute predicted PASI responses, including the median and 95% credible intervals for both the fixed effects and random effects analyses for each PASI level, that is, PASI 50, PASI 75, PASI 90 and PASI 100.	Fixed effect and random effects are both in: placeboAdj_treatment_effects.xslx
Additional justification for the above statement, including reference to goodness of fit measures (such as deviance information criterion and residual deviance).	See Table 51 above for the summary. The detailed network diagram, study details and detailed parameters for run and convergence values for fixed effect and random effects models are provided in the file: placAdj_parameters_convergence.xlsx
Table summarising placebo response rates for the PASI outcomes for all the trials included in the network meta-analysis.	See Table 52 above and also placebo_responses_summary.xlsx
Please provide all the files required to run all Stage I analyses and additional requested sensitivity analyses (see below) in WinBUGS, including data, model and initial values for every chain.	Fixed effect file: FE_weeks1216_placeboAdj.txt Random effects file: RE_weeks1216_placeboAdj Also see folder code_stage1.zip for all of the WINBUGs files for all of the analyses

Abbreviations: PASI: Psoriasis Area and Severity Index.

Sensitivity analyses

A13. PRIORITY QUESTION. CS, section B.2.9, "Results of stage I: sensitivity analyses – results" (page 76). The company submission provides 2 sensitivity analyses at stage 1: "including data from 12 weeks only" and "examining the impact of placebo adjustment".

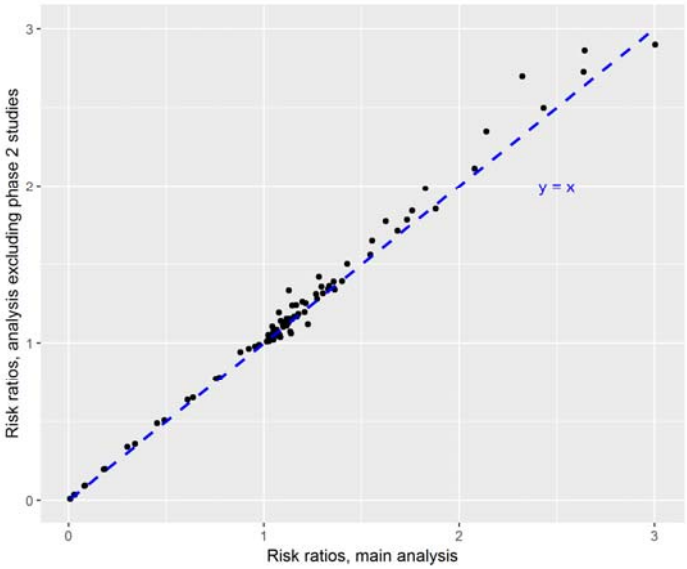
- For the following additional sensitivity analyses:
    - sensitivity analysis 1: excluding phase 2 trials
    - sensitivity analysis 2: excluding unlicensed doses and comparators not included in the NICE scope
    - sensitivity analysis 3: including infliximab trials
- please provide the following results, along with associated goodness of fit statistics:
    - tables summarising the risk ratios, including the median and 95% credible intervals for both the fixed effects and random effects analyses, with and without placebo adjustment, for the PASI outcomes.
    - tables summarising the absolute predicted PASI responses, including the median and 95% credible intervals for both the fixed effects and random effects analyses, with and without placebo adjustment, for each PASI level, that is, PASI 50, PASI 75, PASI 90 and PASI 100.
- Please provide all the files required to run all Stage I analyses and additional requested sensitivity analyses (see above) in WinBUGS, including data, model and initial values for every chain.

Response:

a) Sensitivity analysis, stage 1 excluding phase 2 studies

This network was based on a reduced version of the main network at stage 1 (weeks 12 to 16) where phase 2 studies have been removed. There is some evidence that this network offers a more precise estimation of risk ratios if analysed by a random effects model with placebo adjustment. However, risk ratio estimates are not far apart: Risk ratios of the comparators relative to tildrakizumab 100mg at Week 0 and 4 and tildrakizumab 200mg at Week 0, and 4 as calculated by the "no phase 2" network and four models (fixed effect / random effects and with / without placebo adjustment) are included in the 95% credibility interval in their respective counterpart from the main analysis. The similarity is supported visually by the plot in Figure 2 where the risk ratio estimates from the main network and sensitivity analysis network are plotted as pairs. Risk ratios in Figure 2 are restricted to those for treatments of interest versus both doses of tildrakizumab (random effects model, with placebo adjustment). The points are placed around the diagonal line, which signifies similarity.

Figure 2: Risk ratios, main analysis v "excluding phase 2 studies", random effects model with placebo adjustment, all PASI levels, treatments of interest v tildrakizumab (both doses)



The details are as follows.

For this sensitivity analysis the network from the main analysis stage 1 was reduced by removing phase 2 studies. The following studies were removed:

- Gottlieb et al 2003
- LOTUS
- M02-528
- Nakagawa et al 2016
- P05495- Papp 2015
- Papp et al 2012
- X-PLORE
- CORE
- Ohsuki 2017
- Asahina et al 2010

Four models were employed to analyse the network:

- Fixed effect model, no placebo adjustment
- Fixed effect model, with placebo adjustment
- Random effects model, no placebo adjustment
- Random effects model, with placebo adjustment

Regarding model fit, the random effects model with placebo adjustment provided the best fit (as measured by the deviance information criterion [DIC]). Table 54 shows a summary of model fit statistics.

Table 54: Model fit for sensitivity analysis: excluding phase 2 studies

Model	DIC	pD
Fixed, no placebo adjustment	[redacted]	[redacted]
Fixed, placebo adjustment	[redacted]	[redacted]
Random, no placebo adjustment	[redacted]	[redacted]
Random, placebo adjustment	[redacted]	[redacted]

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

Contrary to the main analysis, the placebo adjustment in combination with the random effects model does improve the model fit, although the difference is small. The difference in DIC is 1.67, and anything less than 5 is considered to be a small difference.

Note that the comparators of interest are:

- Placebo
- Tildrakizumab 100mg Week 0, 4,
- Tildrakizumab 200mg Week 0, 4
- Adalimumab 40mg Q2Wld
- Brodalumab 210mg Q2W
- Etanercept 50mg QW
- Guselkumab 100mg Q8W
- Ixekizumab 80mg Q4W
- Secukinumab 300mg Q4W
- Ustekinumab 45mg Week 0, 4, Q12W
- Ustekinumab 45_90mg Week 0, 4, Q12W, 16, (28)
- Ustekinumab 90mg Week 0, 4, Q12W

In order to compare the outcome of the “no phase 2” network to the outcome of the main analysis, the width of 95% credibility intervals were compared. Table 55 summarises the calculations.

- Column “Main, t100” calculates the average width of credibility intervals for risk ratios of comparators relative to tildrakizumab 100mg Week 0, 4 in the main analysis.
- Column “No phase 2 studies, t100” calculates the average width of credibility intervals for risk ratios of comparators relative to tildrakizumab 100mg Week 0, 4 in the “no phase 2 studies” analysis.
- Column “Main, t200” calculates the average width of credibility intervals for risk ratios of comparators relative to tildrakizumab 200mg Week 0, 4 in the main analysis.
- Column “No phase 2 studies, t200”calculates the average width of credibility intervals for risk ratios of comparators relative to tildrakizumab 200mg Week 0, 4 in the “no phase 2 studies” analysis.

Table 55: Mean width of 95% credibility intervals for risk ratios, comparators v tildrakizumab 100mg / 200mg

PASI level	Model	Main, t100	No phase 2 studies, t100	Main, t200	No phase 2 studies, t200
PASI 50	random, no placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50	random, placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	random, no placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	random, placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	random, no placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	random, placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	random, no placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	random, placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PASI: Psoriasis Area and Severity Index.

In general, credibility intervals are smaller within the main analysis without placebo adjustment, and larger with placebo adjustment, when compared to their counterparts in “no phase 2 studies”. Given that random effects models fare best in terms of model fit, random effects model with placebo adjustment for the “no phase 2” network could be considered if this network is considered to be more appropriate.

Further details (risk ratios, treatment effects) are provided in the accompanying file: **Additional references and files / Text files and excel spreadsheets / A13 Excluding Phase 2 studies**. Table 56 lists the contents of this file.

Table 56: Files relating to the sensitivity analysis excluding phase 2 trials

Content	Filename
Network diagrams, study details, parameters for runs and convergence values. For fixed effect and random effects models, for placebo adjusted and non-placebo adjusted networks	noP2_parameters_convergence.xlsx
Absolute predicted PASI responses, including the median and 95% credible intervals for both the fixed effects and random effects analyses for PASI 50, PASI 75, PASI 90 and PASI 100.	placeboAdj_treatment_effects.xlsx
WINBUGS code and data	No placebo adjusted, Fixed effect: FE_noP2_noPlacAdj.txt No placebo adjusted, Random effects: RE_noP2_noPlacAdj.txt Placebo adjusted, fixed effect: FE_noP2_PlacAdj.txt Placebo adjusted, random effects: RE_noP2_placAdj.txt
Risk ratios for PASI 50, 75, 90 and 100	No placebo adjusted, Fixed effect: NoP2_noPlacAdj_Fixed.xlsx No placebo adjusted, Random effects: NoP2_noPlacAdj_Random.xlsx

Content	Filename
	Placebo adjusted, fixed effect: NoP2_PlacAdj_Fixed.xlsx Placebo adjusted, random effects: NoP2_PlacAdj_Random.xlsx

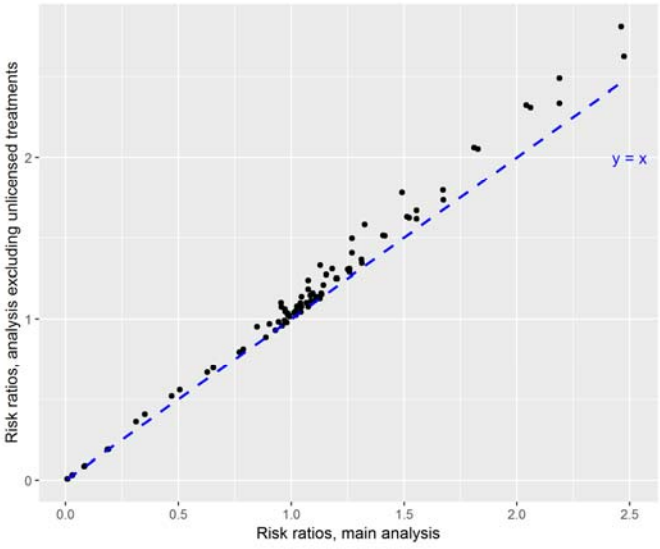
Abbreviations: PASI: Psoriasis Area and Severity Index.

b) Sensitivity analysis, stage 1 excluding unlicensed treatments

This network was based on a reduced version of the main network at stage 1 (Weeks 12 to 16), where unlicensed treatments were removed. The network appears to be more homogeneous, however, this is off-set by larger credibility intervals due to a smaller network.

The estimated risk ratios are not strongly affected by the exclusion of unlicensed treatments from the network. For all four model variants (fixed effect / random effects and with / without placebo adjustment) of this sensitivity analysis, the risk ratios of the comparators relative to tildrakizumab 100mg at Week 0 and 4 and tildrakizumab 200mg at Week 0 and 4 are included in the 95% credibility interval in their respective counterpart from the main analysis. The similarity is supported visually by Figure 3 where the risk ratio estimates from the main network and sensitivity analysis network are plotted as pairs. Risk ratios in Figure 3 are restricted to those for treatments of interest versus both doses of tildrakizumab (random effects model, without placebo adjustment). The points are placed around the diagonal line, which signifies similarity.

Figure 3: Risk ratios, main analysis v "excluding unlicensed treatments", random effects model without placebo adjustment, all PASI levels, treatments of interest v tildrakizumab (both doses)



The details are as follows.

For this sensitivity analysis the network from the main analysis stage 1 was reduced to the following treatments (i.e. study arms with treatments not in the list were removed):

- Placebo
- Tildrakizumab 100mg Week 0, 4,
- Tildrakizumab 200mg Week 0, 4
- Adalimumab 40mg Q2Wld
- Brodalumab 210mg Q2W
- Etanercept 50mg QW
- Guselkumab 100mg Q8W
- Ixekizumab 80mg Q4W
- Secukinumab 300mg Q4W
- Ustekinumab 45mg Week 0, 4, Q12W
- Ustekinumab 45_90mg Week 0, 4, Q12W, 16, (28)
- Ustekinumab 90mg Week 0, 4, Q12W
- Apremilast 30mg BID
- DMF 729mg max. (240mg TID)

Four models were employed to analyse the network:

- Fixed effect model, no placebo adjustment
- Fixed effect model, with placebo adjustment
- Random effects model, no placebo adjustment
- Random effects model, with placebo adjustment

Regarding model fit, the random effects model without placebo adjustment fares best (as measured by the deviance information criterion [DIC]). Table 57 shows a summary of model fit statistics.

Table 57: Model fit for sensitivity analysis: excluding unlicensed treatments

Model	DIC	pD
Fixed, no placebo adjustment	[redacted]	[redacted]
Fixed, placebo adjustment	[redacted]	[redacted]
Random, no placebo adjustment	[redacted]	[redacted]
Random, placebo adjustment	[redacted]	[redacted]

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

However, the exclusion of unlicensed treatments lets the fixed effect model without placebo adjustment look relatively close to the random effects model without placebo adjustment in terms of model fit. Therefore, this network appears to be more homogeneous than the main network, where the difference between the fixed effects and random effects model was larger. Similar to the main analysis, the placebo adjustment models do not improve the fit.

In order to compare the outcome of the “licensed treatments” network to the outcome of the main analysis, the width of 95% credibility intervals were compared. Table 58 summarises the calculations.

- Column “Main, t100” calculates the average width of credibility intervals for risk ratios of comparators (first 12 treatments in list above) relative to tildrakizumab 100mg Week 0, 4 in the main analysis.

- Column “Licensed treatments, t100”calculates the average width of credibility intervals for risk ratios of comparators relative to tildrakizumab 100mg Week 0, 4 in the “licensed treatments” analysis.
- Column “Main, t200” calculates the average width of credibility intervals for risk ratios of comparators relative to tildrakizumab 200mg Week 0, 4 in the main analysis.
- Column “Licensed treatments, t200”calculates the average width of credibility intervals for risk ratios of comparators relative to tildrakizumab 200mg Week 0, 4 in the “licensed treatments” analysis.

Table 58: Mean width of 95% credibility intervals for risk ratios, comparators v tildrakizumab 100mg/200mg

PASI level	Model	Main, t100	Licensed treatments, t100	Main, t200	Licensed treatments, t200
PASI 50	random, no placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50	random, placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	random, no placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	random, placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	random, no placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	random, placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	random, no placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	random, placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PASI: Psoriasis Area and Severity Index.

In general, credibility intervals are smaller within the main analysis.

Further details (risk ratios, treatment effects) are provided in the accompanying file: **Additional references and files / Text files and excel spreadsheets / A13 Excluding unlicensed treatments**. The contents of this file are described in Table 59.

Table 59: Files relating to the sensitivity analysis excluding unlicensed doses and comparators

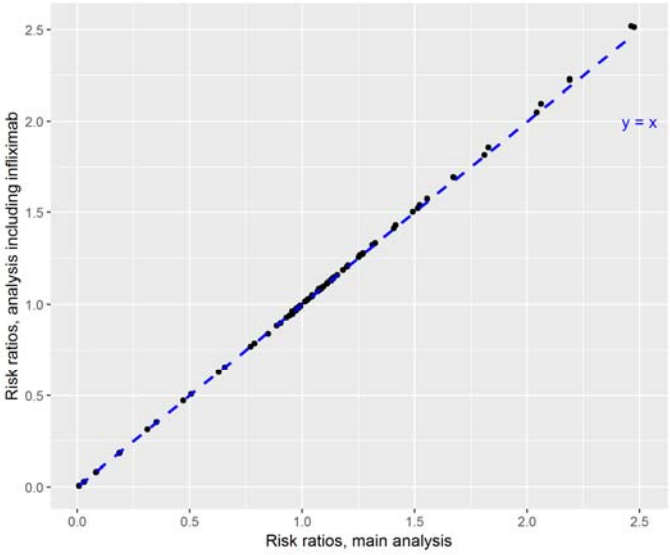
Content	Filename
Network diagrams, study details, parameters for runs and convergence values. For fixed effect and random effects models, for placebo adjusted and non-placebo adjusted networks	licenced_parameters_convergence.xlsx
Absolute predicted PASI responses, including the median and 95% credible intervals for both the fixed effects and random effects analyses for PASI 50, PASI 75, PASI 90 and PASI 100.	licenced_treatment_effects.xlsx
WINBUGS code and data	No placebo adjusted, Fixed effect: FE_licenced_noPlacAdj.txt No placebo adjusted, Random effects: RE_licenced_noPlacAdj.txt Placebo adjusted, fixed effect: FE_licenced_PlacAdj.txt Placebo adjusted, random effects: RE_licenced_placAdj.txt
Risk ratios for PASI 50, 75, 90 and 100	No placebo adjusted, Fixed effect: Licenced_noPlacAdj_Fixed.xlsx No placebo adjusted, Random effects: Licenced_noPlacAdj_Random.xlsx Placebo adjusted, fixed effect: Licenced_PlacAdj_Fixed.xlsx Placebo adjusted, random effects: Licenced_PlacAdj_Random.xlsx

Abbreviations: PASI: Psoriasis Area and Severity Index.

c) Sensitivity analysis, stage 1 including infliximab

This network was based on an enlarged version of the main network at stage 1 (Weeks 12 to 16), and allows treatment comparisons relative to infliximab. As in other sensitivity analyses, risk ratio estimates change relatively little compared to the main analysis. Risk ratios of the comparators relative to tildrakizumab 100mg at Week 0 and 4 and tildrakizumab 200mg at Week 0 and 4 as calculated by the “incl. infliximab” network and four models (fixed effect / random effects and with / without placebo adjustment) are included in the 95% credibility interval in their respective counterpart from the main analysis. The similarity is supported visually by the plot in Figure 4 where the risk ratio estimates from the main network and sensitivity analysis network are plotted as pairs. Risk ratios in Figure 4 are restricted to those for treatments of interest versus both doses of tildrakizumab (random effects model, without placebo adjustment). The points are placed around the diagonal line, which signifies similarity.

Figure 4: Risk ratios, main analysis v "including infliximab", random effects model without placebo adjustment, all PASI levels, treatments of interest v tildrakizumab (both doses)



Regarding risk ratios as calculated by the model with the best fit (random effects model, no placebo adjustment), tildrakizumab 100mg Week 0, 4 is estimated to be marginally inferior to both infliximab 3mg_kg Week 0, 2, 6, Q8W, and infliximab 5mg_kg, Week 0, 2, 6, Q8W on all PASI levels, while there is no evidence of a difference between tildrakizumab 100mg Week 0, 4 and infliximab 10mg_kg Week 0, 2, 6, Q8W on any PASI level. The fact that no evidence of inferiority could be found to the high dose of infliximab is due to the fact that only one study reports on infliximab 10mg _kg Week 0, 2, 6, Q8W, and this one study does indeed report inferiority of the high dose to the medium dose of infliximab, albeit based on low numbers of study subjects.

Tildrakizumab 200mg Week 0, 4 is estimated to be equal to infliximab 3mg_kg Week 0, 2, 6, Q8W and infliximab 10mg_kg Week 0, 2, 6, Q8W on all PASI levels, and marginally inferior to infliximab 5mg_kg Week 0, 2, 6, Q8W on all PASI levels.

The details are as follows.

For this sensitivity analysis the network from the main analysis stage 1 was enlarged by adding studies including infliximab. The following studies were added:

- Chaudhari et al 2001[1]
- Gottlieb et al 2004[2]
- EXPRESS[3]
- EXPRESS II[4]
- Yang et al 2012[5]
- Torii 2010[6]

All of the infliximab trials reported data at 10 weeks rather than 12 or 16 weeks. We note that Gottlieb 2004 also reported data at 14 weeks but the 14 Week data reported were only for PASI 75 (whereas data were reported for PASI 50, 75 and 90 at 10 weeks). Therefore, in order to conduct the sensitivity analysis requested, data at 10 weeks was included for infliximab.

Four models were employed to analyse the network:

- Fixed effect model, no placebo adjustment
- Fixed effect model, with placebo adjustment
- Random effects model, no placebo adjustment
- Random effects model, with placebo adjustment

Regarding model fit, the random effects model without placebo adjustment fares best (as measured by the deviance information criterion, DIC). Table 60 shows a summary of model fit statistics.

Table 60: Model fit for sensitivity analysis: including infliximab

Model	DIC	pD
Fixed, no placebo adjustment	[redacted]	[redacted]
Fixed, placebo adjustment	[redacted]	[redacted]
Random, no placebo adjustment	[redacted]	[redacted]
Random, placebo adjustment	[redacted]	[redacted]

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

Note that the comparators of interest are the following:

- Placebo
- Tildrakizumab 100mg Week 0, 4,
- Tildrakizumab 200mg Week 0, 4
- Adalimumab 40mg Q2Wld
- Brodalumab 210mg Q2W
- Etanercept 50mg QW
- Guselkumab 100mg Q8W
- Ixekizumab 80mg Q4W
- Secukinumab 300mg Q4W
- Ustekinumab 45mg Week 0, 4, Q12W
- Ustekinumab 45_90mg Week 0, 4, Q12W, 16, (28)
- Ustekinumab 90mg Week 0, 4, Q12W

In order to compare the outcome of the “no phase 2” network to the outcome of the main analysis, the width of 95% credibility intervals were compared. Table 61 summarises the calculations.

- Column “Main, t100” calculates the average width of credibility intervals for risk ratios of comparators relative to tildrakizumab 100mg Week 0, 4 in the main analysis.
- Column “Incl. infliximab, t100” calculates the average width of credibility intervals for risk ratios of comparators relative to tildrakizumab 100mg Week 0, 4 in the “incl. infliximab” analysis.
- Column “Main, t200” calculates the average width of credibility intervals for risk ratios of comparators relative to tildrakizumab 200mg Week 0, 4 in the main analysis.
- Column “Incl. infliximab, t200”calculates the average width of credibility intervals for risk ratios of comparators relative to tildrakizumab 200mg Week 0, 4 in the “incl. infliximab” analysis.

Table 61: Mean width of 95% credibility intervals for risk ratios, comparators v tildrakizumab 100mg / 200mg

PASI level	model	Main, t100	Incl. infliximab, t100	Main, t200	Incl. infliximab, t200
PASI 50	random, no placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50	random, placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	random, no placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	random, placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	random, no placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	random, placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	random, no placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	random, placebo adjustment	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PASI: Psoriasis Area and Severity Index.

In general, credibility intervals are smaller within the main analysis when compared to their counterparts in “incl. infliximab”. There is no evidence that this model is to be preferred to the one in the main analysis, since it does not appear to increase precision.

There is, however, more information included: namely risk ratios relative to infliximab, which were absent in the main analysis. The risk ratios are connected via placebo to the rest of the network.

Further details (risk ratios, treatment effects) are provided in in the accompanying file: **Additional references and files / Text files and excel spreadsheets / A13 Including infliximab**. The content of this file is listed in Table 62.

Table 62: Files relating to the sensitivity analysis including infliximab

Content	Filename
Network diagrams, study details, parameters for runs and convergence values. For fixed effect and random effects models, for placebo adjusted and non-placebo adjusted networks	infliximab_stage1_parameters_convergence.xlsx
Absolute predicted PASI responses, including the median and 95% credible intervals for both the fixed effects and random effects analyses for PASI 50, PASI 75, PASI 90 and PASI 100.	infliximab_stage1_treatment_effects.xlsx
WINBUGS code and data	No placebo adjusted, Fixed effect: FE_infl_stage1_noPlacAdj.txt No placebo adjusted, Random effects: RE_infl_stage1_noPlacAdj.txt Placebo adjusted, fixed effect: FE_infl_stage1_PlacAdj.txt Placebo adjusted, random effects: RE_infl_stage1_placAdj.txt

Risk ratios for PASI 50, 75, 90 and 100	No placebo adjusted, Fixed effect: Infliximab_stage1_noPlacAdj_Fixed.xlsx No placebo adjusted, Random effects: Infliximab_stage1_noPlacAdj_Random.xlsx Placebo adjusted, fixed effect: Infliximab_stage1_PlacAdj_Fixed.xlsx Placebo adjusted, random effects: Infliximab_stage1_PlacAdj_Random.xlsx
Data file for infliximab trials	Additional infliximab data used in the sensitivity analysis.docx
Relative risks of infliximab and other comparator treatments using NMA including infliximab (random effects, non-placebo-adjusted data)	Relative risks_infliximab_comparators.docx

Abbreviations: PASI: Psoriasis Area and Severity Index.

Additional sensitivity analyses

Two additional sensitivity analyses were run to provide additional information on the inclusion of infliximab within the network: All files relating to these analyses and a summary of the results are included in the '**Additional references and files**' accompanying this response:

- Additional analysis 1: Sensitivity analysis, including infliximab and excluding unlicensed treatments (available in **Q13 Additional analysis 1**).
- Additional analysis 2: Sensitivity analysis, including infliximab and stage 3 (Weeks 24 to 28) (available in **Q13 Additional analysis 2**).

References for Question A13:

1. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet*. 2001 Jun 9;357(9271):1842-7. (Provided with this response)
2. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, Bala M, Marano CW, Menter A. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol*. 2004 Oct;51(4):534-42. (Provided with this response)
3. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, Li S, Dooley LT, Griffiths CE; EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet*. 2005 Oct 15-21;366(9494):1367-74. (Provided with this response)
4. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol*. 2007;56:31.e1–.e15. (Provided with this response)
5. Yang HZ, Wang K, Jin HZ, Gao TW, Xiao SX, Xu JH, Wang BX, Zhang FR, Li CY, Liu XM, Tu CX, Ji SZ, Shen Y, Zhu XJ. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. *Chin Med J (Engl)*. 2012 Jun;125(11):1845-51. (Provided with this response)

6. Torii H, Nakagawa H; Japanese Infliximab Study investigators. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicentre trial. *J Dermatol Sci*. 2010 Jul;59(1):40-9. (Provided with this response)

Stage III analysis – characteristics of data source

A14. PRIORITY QUESTION. CS, section B.2.9 (page 66) and Appendices, Appendix D.8, Table 14. Table 14 provides PASI data for 24 or 28 weeks, which are used in the stage III network meta-analysis. Please clarify, by adding extra columns to Table 14, whether the data are from:

- a blinded, controlled phase of the study
- an uncontrolled, blinded phase of the study
- an uncontrolled, unblinded phase of the study.

Response:

Table 14 from Appendix D.8 has been amended as requested and a revised version is provided in Table 63 below. 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.

Note that the reference numbers in Table 63 relate to the references in the original submission (Appendix D).

Table 63: Trials included in the NMA: outcomes and results: PASI data for Weeks 24 or 28

Trial name	Time point (weeks)	Analysis population	Study design for long term data collection	Treatment	N analysed	PASI 50	PASI 75	PASI 90	PASI 100
ACCEPT[3]	NR	NR	NA	Ustekinumab 45mg wk 0, 4, 12	NR	NR	NR	NR	NR
				Ustekinumab 90mg wk 0, 4, 12	NR	NR	NR	NR	NR
				Etanercept 50mg BIW	NR	NR	NR	NR	NR
AMAGINE 1[17]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Brodalumab 210mg Q2W	NR	NR	NR	NR	NR
				Brodalumab 140mg Q2W	NR	NR	NR	NR	NR
AMAGINE 2[31]	24	ITT	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Brodalumab 210mg Q2W	168	NR	143	126	91
				Ustekinumab 45/90mg wk 0, 4, 12	289	NR	199	162	102
				Brodalumab 140mg Q2W	NR	NR	NR	NR	NR
AMAGINE 3[35]	24	ITT	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Brodalumab 210mg Q2W	171	NR	143	123	96
				Ustekinumab 45/90mg wk 0, 4, 12	301	NR	205	159	96
				Brodalumab 140mg Q2W	NR	NR	NR	NR	NR
Asahina et al 2010[40]	24	ITT	Blinded and controlled	Placebo	46	9	6	2	NR
				Adalimumab 40mg Q2W	43	33	30	19	NR
				Adalimumab 40mg Q2W (no loading dose)	38	28	25	20	NR
				Adalimumab 80mg Q2W	42	36	34	28	NR
Bissonnette et al 2013[43]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Adalimumab 40mg Q2W	NR	NR	NR	NR	NR
BRIDGE [45]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				DMF maximum 720mg (240mg TID)	NR	NR	NR	NR	NR
				Fumaderm maximum 720mg (240mg TID)	NR	NR	NR	NR	NR

Trial name	Time point (weeks)	Analysis population	Study design for long term data collection	Treatment	N analysed	PASI 50	PASI 75	PASI 90	PASI 100
CHAMPION[47]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Adalimumab 40mg Q2W	NR	NR	NR	NR	NR
				Methotrexate 7.5-25mg QW	NR	NR	NR	NR	NR
CLEAR[67]	24	NR	Blinded and controlled	Secukinumab 300mg Q4W	163	NR	NR	NR	73
				Ustekinumab 45/90mg wk 0, 4, 12	148	NR	NR	NR	50
CORE[82]	24	ITT	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Apremilast 10mg BID	89	34	16	4	0
				Apremilast 20mg BID	87	43	23	7	0
				Apremilast 30mg BID	88	58	35	13	0
ERASURE[87]	28	ITT	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Secukinumab 300mg Q4W	245	NR	203	168	107
				Secukinumab 150mg Q4W	243	NR	176	129	59
ESTEEM 1[117]	28	FAS	Blinding unclear, uncontrolled	Placebo	NR	NR	NR	NR	NR
				Apremilast 30mg BID	562	NR	173	NR	NR
ESTEEM 1[117]	28	FAS	Blinding unclear, uncontrolled	Placebo	NR	NR	NR	NR	NR
				Apremilast 30mg BID	274	NR	71	NR	NR
FEATURE[155]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Secukinumab 300mg Q4W	NR	NR	NR	NR	NR
				Secukinumab 150mg Q4W	NR	NR	NR	NR	NR
FIXTURE[87]	28	ITT	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Secukinumab 300mg Q4W	323	NR	274	235	129
				Etanercept 50mg BIW for 12 weeks then QW	323	NR	206	129	40
				Secukinumab 150mg Q4W	327	NR	247	183	77
	24	ITT		Placebo	55	7	3	0	NR

Trial name	Time point (weeks)	Analysis population	Study design for long term data collection	Treatment	N analysed	PASI 50	PASI 75	PASI 90	PASI 100
Gottlieb et al 2003[181]			Unblinded and uncontrolled	Etanercept 25mg BIW	57	44	32	12	NR
Igarashi et al 2012[1828]	28	ITT	Blinding unclear, controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Ustekinumab 45mg wk 0, 4, 12	64	NR	44	27	NR
				Ustekinumab 90mg wk 0, 4, 12	59	NR	42	34	NR
JUNCTURE[186]	28	NR	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Secukinumab 300mg Q4W	60	NR	57	45	29
				Secukinumab 150mg Q4W	61	NR	48	37	25
Leonardi et al 2003[194]	24	ITT	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Etanercept 50mg QW	162	113	71	32	NR
				Etanercept 50mg BIW	164	127	97	49	NR
				Etanercept 25mg QW	160	92	40	9	NR
Liberate[196]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Etanercept 50mg QW	NR	NR	NR	NR	NR
				Apremilast 30mg BID	NR	NR	NR	NR	NR
LOTUS[212]	28	ITT	Blinding unclear, uncontrolled	Placebo	NR	NR	NR	NR	NR
				Ustekinumab 45mg wk 0, 4, 12	153	151	140	123	62
M02-528[217]	24	mITT	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Adalimumab 40mg Q2W	45	NR	29	NR	6
				Adalimumab 40mg QW	50	NR	36	NR	NR
Nakagawa et al 2016[219]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Brodalumab 210mg Q2W	NR	NR	NR	NR	NR
				Brodalumab 140mg Q2W	NR	NR	NR	NR	NR
				Brodalumab 70mg Q2W	NR	NR	NR	NR	NR

Trial name	Time point (weeks)	Analysis population	Study design for long term data collection	Treatment	N analysed	PASI 50	PASI 75	PASI 90	PASI 100
Ohtsuki[221]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Apremilast 20mg BID	NR	NR	NR	NR	NR
				Apremilast 30mg BID	NR	NR	NR	NR	NR
Papp 2015 P05495[2]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Tildrakizumab 100mg wk 0, 4	NR	NR	NR	NR	NR
				Tildrakizumab 200mg wk 0, 4	NR	NR	NR	NR	NR
				Tildrakizumab 25mg wk 0, 4	NR	NR	NR	NR	NR
				Tildrakizumab 5mg wk 0, 4	NR	NR	NR	NR	NR
Papp et al 2005[225]	24	ITT	Blinding unclear, uncontrolled	Placebo	NR	NR	NR	NR	NR
				Etanercept 50mg QW	196	88	NR	NR	NR
				Etanercept 50mg BIW for 12 weeks then QW	194	105	NR	NR	NR
Papp et al 2012[227]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Brodalumab 210mg Q2W	NR	NR	NR	NR	NR
				Brodalumab 70mg Q2W	NR	NR	NR	NR	NR
				Brodalumab 140mg Q2W	NR	NR	NR	NR	NR
				Brodalumab 280mg Q4W	NR	NR	NR	NR	NR
PEARL[237]	28	ITT	Blinding unclear, uncontrolled	Placebo	NR	NR	NR	NR	NR
				Ustekinumab 45mg wk 0, 4, 12	58	49	42	35	12
PHOENIX 1[241]	28	ITT	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Ustekinumab 45mg wk 0, 4, 12	250	228	178	123	52
				Ustekinumab 90mg wk 0, 4, 12	243	234	191	135	71
PHOENIX 2[273]	28	ITT	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Ustekinumab 45mg wk 0, 4, 12	397	369	276	178	74
				Ustekinumab 90mg wk 0, 4, 12	400	380	314	217	118

Trial name	Time point (weeks)	Analysis population	Study design for long term data collection	Treatment	N analysed	PASI 50	PASI 75	PASI 90	PASI 100
ReSURFACE 1[283]	28	mITT	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Tildrakizumab 100mg wk 0, 4	299	NR	229	147	67
				Tildrakizumab 200mg wk 0, 4	298	NR	236	170	91
ReSURFACE 2[283]	28	mITT	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Tildrakizumab 100mg wk 0,4	294	[redacted]	216	161	66
				Tildrakizumab 200mg wk 0,4	299	[redacted]	217	169	79
				Etanercept 50mg BIW for 12 weeks then QW	289	[redacted]	155	85	31
REVEAL[287]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Adalimumab 40mg Q2W	NR	NR	NR	NR	NR
Trying et al 2006[321]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Etanercept 25mg BIW	NR	NR	NR	NR	NR
ultIMMA-1[325]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Risankizumab 150mg wk 0, 4, 16, 28, 40	NR	NR	NR	NR	NR
				Ustekinumab 45/90mg wk 0, 4, 12	NR	NR	NR	NR	NR
ultIMMA-2[325]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Risankizumab 150mg wk 0, 4, 16, 28, 40	NR	NR	NR	NR	NR
				Ustekinumab 45/90mg wk 0, 4, 12	NR	NR	NR	NR	NR
UNCOVER-1[328]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Ixekizumab 80mg Q4W	NR	NR	NR	NR	NR
				Ixekizumab 80mg Q2W	NR	NR	NR	NR	NR
UNCOVER-2[328,353]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Ixekizumab 80mg Q4W	NR	NR	NR	NR	NR
				Etanercept 50mg BIW	NR	NR	NR	NR	NR
				Ixekizumab 80mg Q2W	NR	NR	NR	NR	NR

Trial name	Time point (weeks)	Analysis population	Study design for long term data collection	Treatment	N analysed	PASI 50	PASI 75	PASI 90	PASI 100
UNCOVER-3[328,353]	24	ITT	Not blinded, uncontrolled	Placebo	NR	NR	NR	NR	NR
				Ixekizumab 80mg Q4W	386	NR	320	284	189
				Etanercept 50mg BIW	NR	NR	NR	NR	NR
				Ixekizumab 80mg Q2W for 12 weeks then Q4W	385	NR	339	301	214
UNVEIL[406]	NR	NR	NA	Placebo	NR	NR	NR	NR	NR
				Apremilast 30mg BID	NR	NR	NR	NR	NR
Van de Kerkhof et al 2008[411]	24	ITT	Not blinded, uncontrolled	Placebo	NR	NR	NR	NR	NR
				Etanercept 50mg QW	90	75	64	38	NR
VOYAGE 1[413]	24	ITT	Blinded and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Adalimumab 40mg Q2W	334	NR	241	177	83
				Guselkumab 100mg Q8W	329	NR	300	264	146
VOYAGE 2[427]	24	ITT	Blinded and controlled	Guselkumab 100 mg wk 16, 20	496	NR	442	373	219
				Adalimumab 80 mg at wk 0, 40mg wk1, 40mg Q2W	248	NR	176	136	66
X-PLORE[430]	28	ITT	Partially blinded (adalimumab not blinded) and controlled (placebo arm dropped)	Placebo	NR	NR	NR	NR	NR
				Adalimumab 40mg Q2W	43	NR	32	22	10
				Guselkumab 100mg Q8W	42	NR	40	35	24
				Guselkumab 5mg Q12W	41	NR	20	14	9
				Guselkumab 15mg Q8W	42	NR	37	20	15
				Guselkumab 50mg Q12W	42	NR	36	31	24
				Guselkumab 200mg Q12W	42	NR	39	29	10
Zhang et al 2015[435]	24	ITT	Not blinded, uncontrolled	Placebo	NR	NR	NR	NR	NR
				Adalimumab 40mg Q2W	333	NR	292	NR	NR

Abbreviations: BID: twice daily; BIW: twice weekly; FAS: full analysis set; ITT: intention to treat; ld: loading dose; mITT: modified intention to treat; NR: not reported; PASI: Psoriasis Area and Severity Index; QW: weekly; Q2W: every two weeks; Q4W: every four weeks; Q8W: every eight weeks; Q12W: every twelve weeks; TID: three times daily; wk: week

Appendix L.8

A15. PRIORITY QUESTION. Appendices, Appendix L.8, Tables 84-91 (pages 403-410). Tables 84 to 91 provide the results of the network meta-analysis at 24/28 weeks. Please compare these results with controlled direct comparisons at 24/28 weeks, providing a table of the trials, comparisons, available data and risk ratios from the direct comparisons.

Response:

The analyses have been conducted with the results in the accompanying Excel spreadsheet labelled **Q15 direct and indirect data_w28.xlsx**.

Table 99 in the spreadsheet displays inconsistency information about the Weeks 24 to 28 (stage III) analysis using the fixed effect model. Inconsistencies arise from disagreement of direct and indirect evidence within a network.

For a given pair of treatments (treatment 1, treatment 2) some studies might report results for both treatments, some studies might report results on only one of the two treatments, and some studies will not have any of the two treatments included. The “direct evidence” network for the pair of treatments consists of those studies where both treatments are present, and any additional arms are removed. The “indirect evidence” network contains all the other studies. A conflict between direct and indirect evidence networks can only arise if both treatments are included in the “indirect evidence network”.

The first three columns explain which treatment pairs are being examined at which PASI level. The following explains the other columns in more detail.

- p_{sym}: This measures 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.
- Risk ratio, direct: the risk ratio as calculated by the direct evidence network.
- Risk ratio, indirect: the risk ratio as calculated by the indirect evidence network.
- Treatment effect T1, direct: treatment effect for first treatment as calculated by the direct evidence network.
- Treatment effect T1, indirect: treatment effect for first treatment as calculated by the indirect evidence network.
- Treatment effect, T2, direct/indirect: same as above, but for the second treatment.
- Number of studies, direct: the number of studies in the direct network which also report on the given PASI level as mentioned in “PASI” column.
- Number of studies, indirect: the number of studies in the indirect network.
- I^2: statistics for heterogeneity (reported in a different table) – the lower this value, the less heterogeneity is present in the direct network for the given PASI level. This value might not exist since the direct network needs to consist of at least two studies in order to calculate this statistic.
- Studies with direct comparisons: List of studies comprised in the direct evidence network, including reported risk ratio.

Table 100 in the spreadsheet is similar to Table 99, but uses the random effects model.

Note: Two studies report a “NR” (not reported) value for PASI 90, placebo versus ustekinumab 45_90mg Wk 0, 4, Q12W, 16, (28). The programme code counted this as two studies reporting actual values. This is a situation that is unique for these two studies and occurs nowhere else. The direct network imputed a value (given that other PASI levels were present) for this PASI level. This should have been suppressed in the table, but was only spotted as the table was being prepared. This case is highlighted in yellow in the table.

Appendix L.12

A16 Appendices, Appendix L.12, Forest plots (pages 566-605). Appendix L.12 provides forest plots of the ‘relative risk and 95% CI’ for each direct placebo comparison. Please clarify whether these are the results of the network meta-analysis or of separate pairwise meta-analyses.

Response:

The forest plots on pages 566 to 605 of the Appendices document display results of the network meta-analysis.

Section B: Clarification on cost-effectiveness data

Comparators

B1. PRIORITY QUESTION. CS, section B.3.2, ‘Intervention technology and comparators’ (page 95). The company submission states that “infliximab is included in the NICE pathway for very severe psoriasis and is also not a relevant comparator and will not compete directly with tildrakizumab”. It is unclear whether the company wishes to make a case for the use of tildrakizumab for this specific ‘very severe’ subgroup (PASI ≥20, DLQI >18) or is seeking a more restrictive positioning compared to other biological treatments that have been compared with infliximab. If the company is not seeking a more restrictive positioning, please provide an additional scenario including infliximab as a potential comparator.

Response:

Infliximab has now been added as an active comparator within the economic model. Within this version of the model relative risk values have been added for infliximab versus tildrakizumab based on the updated NMA described above in order to estimate the relative treatment effect of this intervention in terms of PASI response. These efficacy estimates are based on 5mg/kg infliximab, which is the licensed dose for this treatment.

The costing sheets of the model have also been updated to incorporate infliximab, based on a unit price of £377 for a 100mg vial (for the lowest priced biosimilar of infliximab [Flixabi] in the British National Formulary [BNF] https://bnf.nice.org.uk/medicinal-forms/infliximab.html). The total cost during the induction and maintenance periods have then been estimated based on a required dose of 5mg/kg and a mean patient weight of 88.54kg (the mean weight of all subjects enrolled in the reSURFACE trials). As infliximab is administered intravenously and supplied in vials there is a risk of wastage and this has been accounted for in the results presented below. However, functionality has been included in the economic model to facilitate vial sharing, which equates to no wastage.

Based on a weight of 88.54kg, and accounting for vial wastage, it has been assumed that five vials of infliximab are required with each dose of the treatment. Different dosing schedules have been modelled for the induction (3 doses) and maintenance (1.75 doses) periods, based on information presented in the BNF, equating to total costs per cycle of £5,655 and £3,299 for these two periods, respectively.

The administration and monitoring protocol for infliximab is assumed to be distinct to the other biologic therapies included in the model, based on information presented in previous NICE appraisals in this indication, namely brodalumab (NICE TA511). Based on this appraisal it has been assumed that infliximab patients require one additional outpatient visit, liver function test, full blood count and urea/electrolyte test during the induction period when compared with the other biologics (i.e. 3 per cycle). There are no changes in regards to these resources for the maintenance period. Infliximab patients also require additional outpatient visits for each dose of the treatment as it is administered intravenously and thus needs the supervision of a health care professional. Therefore, patients are assumed to receive 3 additional outpatient visits during the induction period and 1.75 additional visits during each maintenance period to align with the dosing schedule discussed above at a total cost of £103.05 per visit (NHS Ref Costs).

As with all other interventions included in the model, infliximab patients who enter the maintenance phase are at risk of discontinuation with an annual rate of 18.70% (4.67% per cycle) applied, which is aligned with all other interventions.

The results with the inclusion of infliximab have been estimated and are summarised in Table 64. For this analysis, tildrakizumab (sequence 1) was the referent comparator sequence in the incremental analysis (Table 64). A total of five sequences were dominated and can therefore be 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. The piecewise analysis indicates that tildrakizumab is cost-effective versus each individual comparator sequence with a positive net monetary benefit value generated.

Overall, the results of this scenario analysis are similar to the base case analysis and the inclusion of infliximab does not impact on the overall conclusions (i.e. that tildrakizumab is the most cost-effective sequence). All of the comparator sequences were dominated within the fully incremental analysis, and thus would not be considered as cost-effective, with the exception of infliximab, ixekizumab and brodalumab (sequences 9, 6 and 7 respectively). However, the ICER for these sequences are far greater than the cost-effectiveness threshold of £20,000 to £30,000 and, therefore, the tildrakizumab sequence is the most cost-effective option.

Table 64: Results of scenario: inclusion of infliximab as comparator

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
1: Tildrakizumab	[redacted]	[redacted]	£0	0.00	-	-
5: Etanercept	£236,806	[redacted]	[redacted]	[redacted]	Dominated	£2,972
2: Adalimumab	£237,303	[redacted]	[redacted]	[redacted]	Dominated	£1,314
3: Ustekinumab	£238,063	[redacted]	[redacted]	[redacted]	Dominated	£2,063
4: Secukinumab	£246,196	[redacted]	[redacted]	[redacted]	Dominated	£10,044
9: Infliximab	£253,798	[redacted]	[redacted]	[redacted]	£199,148	£15,835
6: Ixekizumab	£265,225	[redacted]	[redacted]	[redacted]	£367,658	£26,668
8: Guselkumab	£265,396	[redacted]	[redacted]	[redacted]	Dominated	£27,373
7: Brodalumab	£267,477	[redacted]	[redacted]	[redacted]	£6,693,147	£28,884

Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; QALY: quality-adjusted life year.

Model structure

Health state

B2. CS, section B.2.9 (pages 63-66) and section B.3.2 'Model structure' (pages 90-92). The network meta-analysis in the company submission includes PASI 100 as a separate outcome. However, its economic model uses a single health state: PASI ≥90. Recent NICE technology appraisals in psoriasis (for example, TA511 and TA442) have used 2 separate states: PASI 90-99 and PASI 100. Please justify why a single state (PASI ≥90) has been used.

Response:

Whilst two recent NICE technology appraisals included a health state for PASI 100, as stated in the questions above, a larger number of previous appraisals have not included this state (i.e. TA103, TA146, TA180, TA350) and the model structures appear to be accepted by either the ERG or committee during those appraisals. Therefore, the decision was made to adopt the most common model structure.

Furthermore, the only impact of the addition of an extra health state would be on the accumulated QALYs (as PASI state does not directly impact on costs). However, as summarised in Table 48 of the company submission for brodalumab, the difference in utility between PASI 90 to 99 and PASI 100 is very small. In this table the following differences are reported: 0.002 (Sherif et al 2017), 0.005 (Pickard et al 2017), 0.009 (TA442) and 0.013 (TA511), which across the four studies equates to a mean difference of 0.007. Therefore, due to the small difference in utility, the addition of a PASI 100 state is not expected to have an impact on the current analysis, particularly given that the key driver of the results are the cost of the treatments themselves.

References for Question B2

- Sherif B, Graham CN, Neidhardt K et al. EQ-5D-3l utilities tariffs: Differences in German and UK utilities and QALYs in patients with moderate to severe psoriasis. *Value in Health*. 2017;20 (5):A331. (Provided with this response)
- Pickard AS, Gooderham M, Hartz S et al. EQ-5D health utilities: exploring ways to improve upon responsiveness in psoriasis. *J Med Econ*. 2017;20(1):19-27. (Provided in original submission reference pack)

Cycle length

B3. CS, section B.3.2 'Model structure' (pages 91-92). The company submission states that in order to simplify the model structure, a 14-week cycle was applied. This is the midpoint of induction periods for other treatments (12 or 16 weeks). Please justify why a shorter cycle length was not used; for example, a 2-week cycle length would have allowed the induction periods of other comparators to precisely match the stopping rules in existing NICE recommendations.

Response:

The use of two-week cycles would have substantially increased the size and complexity of the model, thus increasing the risk of programming errors, so a pragmatic decision was made to use 14-week cycles and decrease the risk of any errors. Efficacy and costs are fully captured in the economic model with a 14-week cycle length.

Stopping rule

B4. PRIORITY QUESTION. CS, section B.2.6.4, 'Appropriate timepoint to assess treatment response' (page 51), section B3.3 (pages 98-101) and section B.3.8.4, 'Scenario 5: alternative efficacy data for all comparators (28 weeks)' (page 142). The company submission states that "it would be biologically implausible, evidently premature, and clinically burdensome to specialists and patients, to implement an assessment and stopping rule at week 12. Therefore, Almirall proposes an assessment time point at 28 weeks". However, its economic model includes an induction period of 14 week, at which point treatment response is assessed.

- Please justify the assumption of a 14 week stopping rule for tildrakizumab in the base-case analysis.
- The company presents a scenario analysis that increased the induction period from 14 to 28 weeks for all treatments.
    - Please present an additional scenario that assumes a 28 week stopping rule for tildrakizumab only.
    - Please include an additional function in the Excel model to allow flexibility to select either a 14 or 28 week induction period for tildrakizumab and a separate function to select either a 14 or 28 week induction period for the comparators.

Response:

Justification of the assumption of a 14 week stopping rule for tildrakizumab in the base-case analysis

The 14 week stopping rule was chosen because for the majority of treatments included in the analysis, 12 to 16 weeks was the time at which the primary outcome measure was assessed during the pivotal studies, including the tildrakizumab reSURFACE studies. It was decided that it was preferable to base the analysis on primary outcome measures as opposed to secondary measures (i.e. outcomes at 28 weeks). Furthermore, the use of 12 to 16 week data leads to conservative outcomes from the perspective of tildrakizumab as shown by the results of the 28 week scenario analysis presented in the cost-effectiveness section of the Almirall submission (Document B), in which the results for tildrakizumab were more favourable when compared with the base case analysis (see Document B, section B.2.13 for details of the proposed 28 week stopping rule).

Scenario that assumes a 28 week stopping rule for tildrakizumab only

In the base case analysis, the time frame for treatment effectiveness data for both the tildrakizumab and the comparator sequence was 14 weeks. As requested by the ERG, 28-week effectiveness and cost data for the tildrakizumab sequence have been applied for this scenario, whilst 14-week effectiveness data was used for all comparator sequences. The rest of the model was unchanged from the base case.

For this scenario, the lowest cost sequence, etanercept (sequence 5), was the referent comparator sequence in the fully incremental analysis (Table 65). Within this analysis 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, indicating that 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.

Table 65: Results of scenario: 28 week effectiveness data (tildrakizumab sequence)

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
5: Etanercept	[redacted]	[redacted]	£0	0.00	-	£1,838
2: Adalimumab	[redacted]	[redacted]	£524	0.1404	£3,731	-£445
3: Ustekinumab	[redacted]	[redacted]	£1,287	0.1409	Dominated	£307
1: Tildrakizumab	[redacted]	[redacted]	[redacted]	[redacted]	£22,689	-
4: Secukinumab	[redacted]	[redacted]	£9,422	0.1486	Dominated	£8,288
6: Ixekizumab	[redacted]	[redacted]	£28,471	0.2955	Dominated	£24,399
8: Guselkumab	[redacted]	[redacted]	£28,567	0.2686	Dominated	£25,154
7: Brodalumab	[redacted]	[redacted]	£30,632	0.2960	Dominated	£26,550

Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; QALY: quality-adjusted life year.

Additional functionality in the Excel model

The additional functionality has been added into the model (revised version provided with this response).

Quality of life

Regression methods

B5. CS, section B.3.4, 'Health-related quality-of-life data used in the cost-effectiveness analysis' (pages 105-106). The company submission used health state utilities based on EQ-5D data at week 12 from reSURFACE1.

- Please provide details of the regression methods used to estimate change in EQ-5D from baseline to 12 weeks.
- Please confirm whether any adjustments were made for baseline EQ-5D and/or other covariates.

Response:

Regression method used to estimate change in EQ-5D from baseline to Week 12

The analysis of EQ-5D in the reSURFACE 1 study was considered exploratory according to the protocol and it was based on descriptive statistics only (please see CSR table results). No regression methods were used.

- CSR for reSURFACE 1 (pages 869-874) Tables 14.2.1-40 and 14.2.1-41: Part 1 and Part 2
- CSR for reSURFACE 1 (pages 874-895) Tables 14.2.1-42, -43, -44, -45, -46, -47: Part 3

Adjustments from baseline EQ-5D and / or other covariates

There were no adjustments from baseline EQ-5D and / or other covariates as no regression models were used to analyse EQ-5D (i.e. the EQ-5D was analysed by means of descriptive statistics).

Reference for Question B5

- Clinical study report for MK-3222 P010 (reSURFACE 1): A 64-week, phase 3, randomized, placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab (SCH 900222/MK-3222), followed by an optional long-term safety extension study, in subjects with moderate-to-severe chronic plaque psoriasis (*Academic in Confidence*). 13 February 2017. (Provided in original submission reference pack).

European valuation set

B6. PRIORITY QUESTION. CS, section B.3.4, 'Health-related quality-of-life data from clinical trials' (page 103). The company submission states that "index utility estimates were calculated based on the EQ-5D data collected in the reSURFACE study using the European valuation set".

- Please revise the EQ-5D analyses using index utility estimates based on the UK value set (Dolan 1997) rather than the European value set.
- Please provide the following additional analyses using the UK value set:
    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 >10 subgroup)
    c) results for a) and b) adjusting for baseline-EQ-5D score.

Response:

Revision of the EQ-5D analyses using index utility estimates based on the UK value set (Dolan 1997)

Within Document B it was stated that index utility estimates were based on EQ-5D collected with the reSURFACE 1 study using the European valuation set. This statement needs to be revised as a follow-up assessment has indicated that the 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 dataset has now been re-analysed such that the UK value set has been applied to all patients. The latest version of the economic model contains these utility data. The new data are 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 0.67 to 0.72. As outlined below this has not had a meaningful impact on the results.

The analysis was re-run with the re-analysed EQ-5D dataset from reSURFACE 1 and for this analysis tildrakizumab (sequence 1) was the referent comparator sequence in the incremental analysis (Table 66). All sequences were dominated with the exception of ixekizumab and brodalumab. These sequences were both more costly and more effective than tildrakizumab and were associated with ICERs of £250,251 and £4,326,207, respectively. The piecewise analysis indicates that tildrakizumab is cost-effective versus each individual comparator sequence with a positive net monetary benefit value generated.

Overall, the results of this scenario analysis are very similar to the base case analysis. All of the comparator sequences were dominated within the fully incremental analysis, and thus would not be considered as cost-effective, with the exception of ixekizumab and brodalumab (sequences 6 and 7 respectively). However, the ICER for these sequences are far greater than the cost-effectiveness threshold of £20,000 to £30,000 and, therefore, the tildrakizumab sequence is the most cost-effective option.

Table 66: Results of scenario: EQ-5D analysis based on UK value set

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
1: Tildrakizumab	[redacted]	[redacted]	£0	0.00	-	-
5: Etanercept	£236,755	[redacted]	[redacted]	[redacted]	Dominated	£2,973
2: Adalimumab	£237,225	[redacted]	[redacted]	[redacted]	Dominated	£1,269
3: Ustekinumab	£237,986	[redacted]	[redacted]	[redacted]	Dominated	£2,020
4: Secukinumab	£246,109	[redacted]	[redacted]	[redacted]	Dominated	£9,992
6: Ixekizumab	£265,118	[redacted]	[redacted]	[redacted]	£250,251	£26,655
8: Guselkumab	£265,225	[redacted]	[redacted]	[redacted]	Dominated	£27,301
7: Brodalumab	£267,279	[redacted]	[redacted]	[redacted]	£4,326,207	£28,806

Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; QALY: quality-adjusted life year.

Results for the full population and for the subgroup with baseline DLQI >10 using the UK value set

The mean utility for the full population and subgroup with DLQI >10 are [redacted] and [redacted], respectively.

Results for PASI 90 to 99 and PASI 100 (full population and DLQI >10 subgroup) using the UK value set

Table 67: Mean utility for the PASI 90 to 99 and PASI 100 subgroups using the UK value set

PASI Group	Full Population	DLQI >10
PASI 90 to 99	[redacted]	[redacted]
PASI 100	[redacted]	[redacted]

Abbreviations: DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area Severity Index.

Analyses using the UK value set adjusting for baseline-EQ-5D score

Ordinary least squares regression was undertaken with EQ-5D score at baseline included as a covariate (completed on the UK value set version). The index utility values following this analysis are [redacted] and [redacted] for the full population and DLQI >10 subgroups, respectively.

The regression analysis was also undertaken to estimate index utility for the PASI 90 to 99 and PASI 100 subgroups, again adjusting for EQ-5D at baseline (for both the full population and those patients with a DLQI >10 at baseline). These utility values are presented in Table 69.

Table 68: Mean utility for the PASI 90 to 99 and PASI 100 subgroups using the UK value set, adjusted for baseline utility

PASI Group	Full Population	DLQI >10
PASI 90 to 99	[redacted]	[redacted]
PASI 100	[redacted]	[redacted]

Abbreviations: DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area Severity Index.

Costs

'Non-responder' costs

B7. CS, section B.3.5 (pages 106-110). The company submission does not include 'non-responder' costs. Please present a scenario analysis incorporating additional costs for 'non-responders' in line with other NICE technology guidance on psoriasis (for example, TA475 and TA442).

Response:

Within this scenario, an additional 'non responder' cost of £229 has been incorporated into the economic model and an additional scenario run to present the results. For this scenario it is assumed that £229 is incurred once per treatment line during the induction cycle for all subjects who achieve a PASI score of <75. A cost of £225 per cycle was identified from TA442 and TA475, and inflated to the 2016/2017 price year using PSSRU inflation indices.

Tildrakizumab (sequence 1) was the referent comparator sequence in the incremental analysis (Table 69). Tildrakizumab was more effective and less costly than, and therefore dominated, etanercept, adalimumab and ustekinumab. Guselkumab was also dominated by tildrakizumab. Ixekizumab and brodalumab were both more costly and more effective than tildrakizumab and were associated with ICERs of £202,508 and £4,541,894, respectively. The piecewise analysis indicates that tildrakizumab is cost-effective versus each individual comparator sequence with a positive net monetary benefit value generated.

Overall, the results of this scenario analysis are similar to the base case analysis. All of the comparator sequences were dominated within the fully incremental analysis, and thus would not be considered as cost-effective, with the exception of ixekizumab and brodalumab (sequences 6 and 7 respectively). However, the ICER for these sequences were £202,508 and £4,541,894, respectively, which are far greater than the cost-effectiveness threshold of £20,000 to £30,000 and, therefore, the tildrakizumab sequence is the most cost-effective option.

Table 69: Results of scenario: inclusion of non-responder costs

Comparator	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully incremental ICER	INMB (£/QALY) Tildrakizumab sequence versus comparator
1: Tildrakizumab	[redacted]	[redacted]	£0	0.00	-	N/A
5: Etanercept	[redacted]	[redacted]	[redacted]	-0.1525	Dominated	£3,656
2: Adalimumab	[redacted]	[redacted]	[redacted]	-0.0121	Dominated	£1,318
3: Ustekinumab	[redacted]	[redacted]	[redacted]	-0.0115	Dominated	£2,069
4: Secukinumab	[redacted]	[redacted]	[redacted]	-0.0038	Dominated	£10,037
6: Ixekizumab	[redacted]	[redacted]	[redacted]	0.1431	£202,508	£26,109
8: Guselkumab	[redacted]	[redacted]	[redacted]	0.1101	Dominated	£26,875
7: Brodalumab	[redacted]	[redacted]	[redacted]	0.1435	£4,541,894	£28,260

Abbreviations: ICER: incremental cost-effectiveness ratio; INMB: incremental net monetary benefit; QALY: quality-adjusted life year

B8. CS, section B.3.5 (page 109). In the base-case analysis, the company uses best supportive care costs based on values adopted in the cost-effectiveness model developed for the NICE clinical guideline on psoriasis (CG153). NICE technology appraisal guidance on psoriasis (for example, TA419 and TA350) recognise the uncertainty and shortcomings of existing sources for resource use for best supportive care but 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). Please provide further justification for estimating best supportive care costs using NICE CG53 rather than Fonia et al.

Response:

Clinicians at an England and Wales Advisory Board stated that the study by Fonia et al. no longer reflects UK clinical practice for best supportive care (BSC) and, in fact, underestimates the cost for this treatment. The value provided in NICE CG153 was the only alternative identified following a targeted review and, as the overall cost was higher than that presented by Fonia et al. it was deemed to be a more appropriate source.

Reference for Question B8.

- Almirall. Data on file. Summary report. Tildrakizumab advisory board (*Academic in Confidence*). March 2018. (Provided in original submission reference pack)

Probabilistic Sensitivity Analyses

B9. PRIORITY QUESTION. CS, section B.3.8 (page 119). The probabilistic sensitivity analysis inputs for PASI outcomes are based on independent distributions, which ignore the correlations between PASI categories and between individual treatments from the network meta-analyses. Please revise the probabilistic sensitivity analysis ensuring that the PASI outcomes are directly informed by the WinBUGS CODA.

Response:

The probabilistic sensitivity analysis in the model has been updated such that the PASI outcomes are directly informed by the WinBUGS CODA with a sample of 3,000 iterations run.

Excel model – Programming error

B10. PRIORITY QUESTION. The percent change calculation used in the model and applied to the population norm age is calculated incorrectly – see details and example below. Please revise and resubmit the Excel model correcting for this error.

Error details:

The submitted model calculates the percent change as:

- Percent change = (V2 – V1)/V2 X 100
- Where V2 = mean PASI score from regression model
- V1 = Population norm utility at baseline age

The correct formula should be:

- Percent change = (V2 – V1)/V1 X 100

Example:

- Formula cell F4 on the Population utility norms sheet = (Utility!AB16-'Population Utility Norms'!$D$4)/Utility!AB16 or (0.67 – 0.871)/0.67 = -30%. Applying this to the start age (46) population utility of 0.871 gives a result of 0.6097 (example: cell I35). However, the calculated utility should equal the mean PASI score from the model when applied to the start age population utility. When using the correct formula, the correct percentage reduction is (0.67 – 0.871)/0.871 = -23.08%. Applying this to the start age population utility of 0.871 = 0.67.

Response:

This error has been corrected in the model and a revised version of the model is provided with this response.

Section C: Textual clarifications and additional points

Best supportive care costs

C1. CS, section B.3.2, Figure 23 (page 92). Please clarify whether the PASI 75-90 and PASI >90 states should refer to PASI 75-89 and PASI ≥90.

Response:

We can confirm that the PASI values should be PASI 75 to 89 and PASI ≥90.

C2. CS, section B.2.9, Table 21 (page 67-69) and Appendices, Appendix D.7, Table 9 (pages 47-52).

- The labelling of the trials in Table 21 in the company submission is not consistent with that in Table 9 in Appendix D. Please amend Table 21 and add the main reference details to Table 21 to make it easier to identify the trials correctly.
- The risankizumab *vs* ustekinumab study labelled “Papp 2017” in Table 9 in Appendix D does not appear in other tables. Please clarify.

Response:

A revised version of Table 21 from Document B is provided below (as Table 70) in which the labels and references have been updated. The reference for Papp 2017/2016a in Table 9 in Appendix D is an error, the correct reference is Papp 2015 P05495 from Table 21.

The labelling of the risankizumab *vs* ustekinumab study in Table 9 of Appendix D is also an error, the study should be listed as Papp 2015 (P05495). A revised version of Table 9 is provided below (as Table 71), which includes corrected references to replace the Papp 2017 entry and the Papp 2005 reference.

The reference numbers included in Table 71 relate to the references in the appendices document to the original submission.

Table 70: Summary of all trials used to conduct the NMA

		Intervention						
Trial identifier	**Main trial reference**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
ACCEPT NCT00454584	Griffiths CEM, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010;362(2):118-28.	Etanercept 50mg BIW	Ustekinumab 45mg wk 0, 4	Ustekinumab 90mg wk 0, 4				
AMAGINE 1 NCT01708590	Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2016;175(2):273-86.	Placebo	Brodalumab 140mg Q2W	Brodalumab 210mg Q2W				
AMAGINE 2 NCT01708603	Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med. 2015;373(14):1318-28	Placebo	Ustekinumab 45mg/90mg wk 0, 4, Q12W	Brodalumab 140mg Q2W	Brodalumab 210mg Q2W			
AMAGINE-3 NCT02786732	Strober B, Langley R, Blicharski T, Paul C, Lacour J-P, Tyring S, et al. AMAGINE-3: a phase 3 efficacy and safety study to evaluate induction and maintenance regimens of brodalumab compared with placebo and ustekinumab in patients with moderate to severe plaque psoriasis. In: 23rd World Congress of	Placebo	Ustekinumab 45mg/90mg wk 1, 4, Q12W	Brodalumab 140mg Q2W	Brodalumab 210mg Q2W			

	Dermatology Vancouver, Canada; 8-13 June 2015.							
Asahina et al 2010 NCT01155570	Asahina A, Nakagawa H, Etoh T, Ohtsuki M, Adalimumab MSG. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a phase II/III randomized controlled study. J Dermatol. 2010;37(4):299-310.	Placebo	Adalimumab 40mg Q2Wld	Adalimumab 40mg Q2W (no loading dose)	Adalimumab 80mg Q2Wld			
Bissonnette et al 2013 NTC00940862	Bissonnette R, Tardif J-C, Harel F, Pressacco J, Bolduc C, Guertin M-C. Effects of the tumor necrosis factor-alpha antagonist adalimumab on arterial inflammation assessed by positron emission tomography in patients with psoriasis: results of a randomized controlled trial. Circ Cardiovasc Imaging. 2013;6(1):83-90.	Placebo	Adalimumab 40mg Q2W					
BRIDGE	Mrowietz U, Szepietowski JC, Loewe R, van de Kerkhof P, Lamarca R, Ocker WG, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm and placebo-controlled trial (BRIDGE). Br J Dermatol. 2017;176(3):615-23.	Placebo	DMF maximum 720mg daily (240mg TID)	Fumaderm maximum 720mg daily (240mg TID)				
CHAMPION NCT00235820	Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the	Placebo	Methotrexate 7.5mg to 25mg QW	Adalimumab 40mg Q2W				

	randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008;158(3):558-66							
CLEAR NCT02074982	Thaci D, Blauvelt A, Reich K, Tsai T-F, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol. 2015;73(3):400-9.	Secukinumab 300mg Q4W	Ustekinumab 45mg / 90mg wk 0, 4, Q12W					
Core Study NCT00773734	Papp K, Cather JC, Rosoph L, Sofen H, Langley RG, Matheson RT, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. The Lancet. 2012;380(9843):738-46.	Placebo	Apremilast 30mg BID	Apremilast 10mg BID	Apremilast 20mg BID			
ERASURE NCT01365455	Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CEM, Papp K, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. 2014;371(4):326-38.	Placebo	Secukinumab 300mg Q4W	Secukinumab 150mg Q4W				
ESTEEM 1 NCT01194219	Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RGB, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (efficacy and safety trial	Placebo	Apremilast 30mg BID					

	evaluating the effects of apremilast in psoriasis [ESTEEM] 1). J Am Acad Dermatol. 2015;73(1):37-49.							
ESTEEM 2 NCT01232283	Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). Br J Dermatol. 2015;173(6):1387-99.	Placebo	Apremilast 30mg BID					
FEATURE NCT01555125	Blauvelt A, Prinz JC, Gottlieb AB, Kingo K, Sofen H, Ruer-Mulard M, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol. 2015;172(2):484-93.	Placebo	Secukinumab 300mg Q4W	Secukinumab 150mg Q4W				
FIXTURE NCT01358578	Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CEM, Papp K, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. 2014;371(4):326-38.	Placebo	Secukinumab 300mg Q4W	Secukinumab 150mg Q4W	Etanercept 50mg BIW / QW			
Gottlieb et al 2003	Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol. 2003;139(12):1627-32.	Placebo	Etanercept 25mg BIW					

Igarashi et al 2012	Igarashi A, Kato T, Kato M, Song M, Nakagawa H. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. J Dermatol. 2012;39(3):242-52.	Placebo	Ustekinumab 45mg wk 0, 4, Q12W	Ustekinumab 90mg wk 0, 4, Q12W				
JUNCTURE NCT01636687	Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015;29(6):1082-90.	Placebo	Secukinumab 300mg Q4W	Secukinumab 150mg Q4W				
Leonardi et al 2003	Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med. 2003;349(21):2014-22.	Placebo	Etanercept 25mg QW	Etanercept 25mg BIW	Etanercept 50mg BIW			
LIBERATE	Reich K, Gooderham M, Green L, Bewley A, Zhang Z, Khanskaya I, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). J Eur Acad Dermatol Venereol. 2017;31(3):507-17.	Placebo	Apremilast 30mg BID	Etanercept 50mg QW				
LOTUS	Zhu X, Zheng M, Song M, Shen YK, Chan D, Szapary	Placebo	Ustekinumab 45mg wk 0, 4					

	PO, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). J Drugs Dermatol. 2013;12(2):166-74.							
M02-528	Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol. 2006;55(4):598-606	Placebo	Adalimumab 40mg Q2W	Adalimumab 40mg QW				
Nakagawa et al 2016 NCT01748539	Nakagawa H, Niiro H, Ootaki K, Japanese brodalumab study g. Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: efficacy and safety results from a phase II randomized controlled study. J Dermatol Sci. 2016;81(1):44-52.	Placebo	Brodalumab 70mg Q2W	Brodalumab 140mg Q2W	Brodalumab 210mg Q2W			
Ohtsuki	Ohtsuki M, Okubo Y, Komine M, Imafuku S, Day RM, Chen P, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of Japanese patients with moderate to severe plaque psoriasis: efficacy, safety and tolerability results from a phase 2b randomized controlled trial. J Dermatol. 2017;44(8):873-84.	placebo	Apremilast 30mg BID	Apremilast 10mg BID				

Papp 2015 (P05495)	Papp K et al. Tildrakizumab (MK-3222), an anti-interleukin-23P19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. Br J Dermatol. 2015;173(4):930-39.	Tildrakizumab 5mg wk 0,4	Tildrakizumab 25mg wk 0,4	Tildrakizumab 100mg wk 0,4	Tildrakizumab 200mg wk 0,4	Placebo		
Papp et al 2005	Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 2005;152(6):1304-1312.	Placebo	Etanercept 25mg BIW	Etanercept 50mg BIW / 25mg BIW				
Papp et al 2012 NCT00975637	Papp KA, Leonardi C, Menter A, Ortonne J-P, Krueger JG, Kricorian G, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. N Engl J Med. 2012;366(13):1181-9.	Placebo	Brodalumab 70mg Q2W	Brodalumab 140mg Q2W	Brodalumab 210mg Q2W	Brodalumab 280mg Q4W		
PEARL	Tsai T-F, Ho J-C, Song M, Szapary P, Guzzo C, Shen Y-K, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). J Dermatol Sci. 2011;63(3):154-63.	Placebo	Ustekinumab 45mg wk 0, 4, Q12W					
PHOENIX 1 NCT00267969	Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind,	Placebo	Ustekinumab 45mg wk 0, 4, Q12W	Ustekinumab 90mg wk 0, 4, Q12W				

	placebo-controlled trial (PHOENIX 1). Lancet. 2008;371(9625):1665-74.							
PHOENIX 2 NCT00307437	Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008;371(9625):1675-84.	Placebo	Ustekinumab 45mg wk 0, 4, Q12W	Ustekinumab 90mg wk 0, 4, Q12W				
ReSURFACE I	Reich K, Papp KA, Blauvelt A, Tyring SK, Sinclair R, Thaci D, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet. 2017;390(10091):276-88.	Placebo	Tildrakizumab 100mg wk 0,4	Tildrakizumab 200mg wk 0,4				
ReSURFACE 2	Reich K, Papp KA, Blauvelt A, Tyring SK, Sinclair R, Thaci D, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet. 2017;390(10091):276-88.	Placebo	Tildrakizumab 100mg wk 0,4 Q12W	Tildrakizumab 200mg wk 0,4 Q12W	Etanercept 50mg BIW / QW			
REVEAL NCT00237887	Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis:	Placebo	Adalimumab 40mg Q2W 80mg loading dose					

	a randomized, controlled phase III trial. J Am Acad Dermatol. 2008;58(1):106-15.							
Trying et al 2006 NCT00111449	Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet. 2006;367(9504):29-35.	Placebo	Etanercept 25mg BIW					
ultIMMa-1 NCT02684370	AbbVie. Risankizumab meets all co-primary and ranked secondary endpoints, achieving significantly greater efficacy versus standard biologic therapies in three pivotal phase 3 psoriasis studies [webpage]. North Chicago: AbbVie; 2017. [cited 11 June 2018]. Available from: https://news.abbvie.com/news/press-releases/risankizumab-meets-all-co-primary-and-ranked-secondary-endpoints-achieving-significantly-greater-efficacy-versus-standard-biologic-therapies-in-three-pivotal-phase-3-psoriasis-studies.htm.	Placebo	Risankizumab 150mg wk 0, 4, 16, 28, 40	Ustekinumab 45mg / 90mg Wk 0, 4,16, 28, 40				
ultIMMa-2 NCT02684357	AbbVie. Risankizumab meets all co-primary and ranked secondary endpoints, achieving significantly greater efficacy versus standard biologic therapies in three pivotal phase 3 psoriasis studies [webpage]. North Chicago: AbbVie; 2017. [cited	Placebo	Risankizumab 150mg wk 0, 4, 16, 28, 40	Ustekinumab 45mg / 90mg wk 0, 4, 16, 28, 40				

	11 June 2018]. Available from: https://news.abbvie.com/news/press-releases/risankizumab-meets-all-co-primary-and-ranked-secondary-endpoints-achieving-significantly-greater-efficacy-versus-standard-biologic-therapies-in-three-pivotal-phase-3-psoriasis-studies.htm.							
UNCOVER-1 NCT01474512	Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med. 2016;375(4):345-56.	Placebo	Ixekizumab 80mg Q4W	Ixekizumab 80mg Q2W				
UNCOVER-2 NCT01597245	Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med. 2016;375(4):345-56. Griffiths CEM, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015;386(9993):541-51.	Placebo	Etanercept 50mg BIW	Ixekizumab 80mg Q4W	Ixekizumab 80mg Q2W			
UNCOVER-3 NCT01646177	Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N	Placebo	Etanercept 50mg BIW	Ixekizumab 80mg Q4W	Ixekizumab 80mg Q2W			

	Engl J Med. 2016;375(4):345-56. Griffiths CEM, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015;386(9993):541-51.							
UNVEIL NCT02555826	Celgene. Study of the efficacy and safety of apremilast (CC-10004), in subjects with moderate plaque psoriasis. Identifier: NCT02555826. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2015. Available from https://clinicaltrials.gov/show/NCT02555826.	Placebo	Apremilast 30mg BID					
Van de Kerkhof et al 2008	van de Kerkhof PCM, Segaert S, Lahfa M, Luger TA, Karolyi Z, Kaszuba A, et al. Once weekly administration of etanercept 50mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. Br J Dermatol. 2008;159(5):1177-85.	Placebo	Etanercept 50mg QW					
VOYAGE 1 NCT02207231	Blauvelt A, Papp KA, Griffiths CEM, Randazzo B, Wasfi Y, Shen Y-K, et al. Efficacy and safety of guselkumab, an anti-	Placebo	Guselkumab 100mg wk 0, 4, 12	Adalimumab 40mg Q2W				

	interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017;76(3):405-17.							
VOYAGE 2 NCT02207244	Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. Journal of the American Academy of Dermatology. 2017;76(3):418-31	Placebo	Adalimumab 80mg at wk 0, 40mg wk1, 40mg Q2W	Guselkumab 100 mg wk 0, 4, 12				
X-PLORE NCT01483599	Gordon KB, Duffin KC, Bissonnette R, Prinz JC, Wasfi Y, Li S, et al. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. N Engl J Med. 2015;373(2):136-44.	Placebo	Guselkumab 5mg Q12W	Guselkumab 15mg Q8W	Guselkumab 50mg Q12W	Guselkumab 100mg Q8W	Guselkumab 200mg Q12W	Adalimumab 40mg Q2W
Zhang et al 2015	Cai L, Gu J, Zheng J, Zheng M, Wang G, Xi LY, et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-	Placebo	Adalimumab 40mg Q2W					

	severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. J Eur Acad Dermatol Venereol. 2017;31(1):89-95.							

Table 71 Studies included in the indirect and mixed treatment comparison (45 studies, 445 documents)

Study	Paper(s) *(main paper in full; additional documents appear in reference list)*
ACCEPT NCT00454584	Griffiths CEM, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010;362(2):118-28. [3] Additional documents: [4-16]
AMAGINE 1 NCT01708590	Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2016;175(2):273-86. [17] Additional documents: [18-30]
AMAGINE 2 NCT01708603	Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med. 2015;373(14):1318-28.[31] Additional documents: [25,32-34]
AMAGINE-3 NCT02786732	Strober B, Langley R, Blicharski T, Paul C, Lacour J-P, Tyring S, et al. AMAGINE-3: a phase 3 efficacy and safety study to evaluate induction and maintenance regimens of brodalumab compared with placebo and ustekinumab in patients with moderate to severe plaque psoriasis. In: 23rd World Congress of Dermatology Vancouver, Canada; 8-13 June 2015. [35] Additional documents: [25,36-39]
Asahina et al 2010 NCT01155570	Asahina A, Nakagawa H, Etoh T, Ohtsuki M, Adalimumab MSG. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a phase II/III randomized controlled study. J Dermatol. 2010;37(4):299-310. [40] Additional documents: [41,42]
Bissonnette et al 2013 NTC00940862	Bissonnette R, Tardif J-C, Harel F, Pressacco J, Bolduc C, Guertin M-C. Effects of the tumor necrosis factor-alpha antagonist adalimumab on arterial inflammation assessed by positron emission tomography in patients with psoriasis: results of a randomized controlled trial. Circ Cardiovasc Imaging. 2013;6(1):83-90. [43] Additional documents: [44]
BRIDGE	Mrowietz U, Szepietowski JC, Loewe R, van de Kerkhof P, Lamarca R, Ocker WG, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm and placebo-controlled trial (BRIDGE). Br J Dermatol. 2017;176(3):615-23. [45] Additional documents: [46]
CHAMPION NCT00235820	Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008;158(3):558-66. [47] Additional documents: [48-66]
CLEAR NCT02074982	Thaci D, Blauvelt A, Reich K, Tsai T-F, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol. 2015;73(3):400-9. [67]

	Additional documents: [68-81]
Core Study NCT00773734	Papp K, Cather JC, Rosoph L, Sofen H, Langley RG, Matheson RT, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. The Lancet. 2012;380(9843):738-46. [82] Additional documents: [83-86]
ERASURE NCT01365455	Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CEM, Papp K, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. 2014;371(4):326-38. [87] Additional documents: [88-116]
ESTEEM 1 NCT01194219	Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RGB, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (efficacy and safety trial evaluating the effects of apremilast in psoriasis [ESTEEM] 1). J Am Acad Dermatol. 2015;73(1):37-49. [117] Additional documents: [118-147]
ESTEEM 2 NCT01232283	Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). Br J Dermatol. 2015;173(6):1387-99. [148] Additional documents: [149-154]
FEATURE NCT01555125	Blauvelt A, Prinz JC, Gottlieb AB, Kingo K, Sofen H, Ruer-Mulard M, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol. 2015;172(2):484-93. [155] Additional documents: [156-163]
FIXTURE NCT01358578	Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CEM, Papp K, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. 2014;371(4):326-38. [87] Additional documents: [101,164-180]
Gottlieb et al 2003	Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol. 2003;139(12):1627-32. [181]
Igarashi et al 2012	Igarashi A, Kato T, Kato M, Song M, Nakagawa H. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. J Dermatol. 2012;39(3):242-52. [182] Additional documents: [183-185]
JUNCTURE NCT01636687	Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015;29(6):1082-90. [186] Additional documents: [158,187-193]
Leonardi et al 2003	Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med. 2003;349(21):2014-22. [194] Additional documents: [195]

LIBERATE	Reich K, Gooderham M, Green L, Bewley A, Zhang Z, Khanskaya I, et al. The efficacy and safety of apremilast, etanercept and placebo in patients with moderate-to-severe plaque psoriasis: 52-week results from a phase IIIb, randomized, placebo-controlled trial (LIBERATE). J Eur Acad Dermatol Venereol. 2017;31(3):507-17. [196] Additional documents: [197-211]
LOTUS	Zhu X, Zheng M, Song M, Shen YK, Chan D, Szapary PO, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). J Drugs Dermatol. 2013;12(2):166-74. [212] Additional documents: [213-216]
M02-528	Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol. 2006;55(4):598-606. [217] Additional documents: [218]
Nakagawa et al 2016 NCT01748539	Nakagawa H, Niiro H, Ootaki K, Japanese brodalumab study g. Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: efficacy and safety results from a phase II randomized controlled study. J Dermatol Sci. 2016;81(1):44-52. [219] Additional documents: [220]
Ohtsuki	Ohtsuki M, Okubo Y, Komine M, Imafuku S, Day RM, Chen P, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of Japanese patients with moderate to severe plaque psoriasis: efficacy, safety and tolerability results from a phase 2b randomized controlled trial. J Dermatol. 2017;44(8):873-84. [221]
Papp 2015 P05495	Papp K et al. Tildrakizumab (MK-3222), an anti-interleukin-23P19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. Br J Dermatol. 2015;173(4):930-39. Additional documents: additional references are outlined below the table.
Papp et al 2005	Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol. 2005;152(6):1304-1312. [225] Additional documents: [226]
Papp et al 2012 NCT00975637	Papp KA, Leonardi C, Menter A, Ortonne J-P, Krueger JG, Kricorian G, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. N Engl J Med. 2012;366(13):1181-9. [227] Additional documents: [228-236]
PEARL	Tsai T-F, Ho J-C, Song M, Szapary P, Guzzo C, Shen Y-K, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). J Dermatol Sci. 2011;63(3):154-63. [237] Additional documents: [238-240]

PHOENIX 1 NCT00267969	Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371(9625):1665-74. [241] Additional documents: [242-272]
PHOENIX 2 NCT00307437	Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008;371(9625):1675-84. [273] Additional documents: [274-282]
ReSURFACE I	Reich K, Papp KA, Blauvelt A, Tyring SK, Sinclair R, Thaci D, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet. 2017;390(10091):276-88. [283]
ReSURFACE 2	Additional documents: [284-286]
REVEAL NCT00237887	Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. J Am Acad Dermatol. 2008;58(1):106-15. [287] Additional documents: [288-320]
Trying et al 2006 NCT00111449	Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet. 2006;367(9504):29-35. [321] Additional documents: [322-324]
ultIMMa-1 NCT02684370	AbbVie. Risankizumab meets all co-primary and ranked secondary endpoints, achieving significantly greater efficacy versus standard biologic therapies in three pivotal phase 3 psoriasis studies [webpage]. North Chicago: AbbVie; 2017. [cited 11 June 2018]. Available from: https://news.abbvie.com/news/press-releases/risankizumab-meets-all-co-primary-and-ranked-secondary-endpoints-achieving-significantly-greater-efficacy-versus-standard-biologic-therapies-in-three-pivotal-phase-3-psoriasis-studies.htm. [325] Additional documents: [326]
ultIMMa-2 NCT02684357	AbbVie. Risankizumab meets all co-primary and ranked secondary endpoints, achieving significantly greater efficacy versus standard biologic therapies in three pivotal phase 3 psoriasis studies [webpage]. North Chicago: AbbVie; 2017. [cited 11 June 2018]. Available from: https://news.abbvie.com/news/press-releases/risankizumab-meets-all-co-primary-and-ranked-secondary-endpoints-achieving-significantly-greater-efficacy-versus-standard-biologic-therapies-in-three-pivotal-phase-3-psoriasis-studies.htm. [325] Additional documents: [327]
UNCOVER-1 NCT01474512	Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med. 2016;375(4):345-56. [328] Additional documents: [328-352]
UNCOVER-2 NCT01597245	Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med. 2016;375(4):345-56. [328]

	Griffiths CEM, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015;386(9993):541-51. [353] Additional documents: [354-382]
UNCOVER-3 NCT01646177	Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med. 2016;375(4):345-56. [328] Griffiths CEM, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015;386(9993):541-51. [353] Additional documents: [383-405]
UNVEIL NCT02555826	Celgene. Study of the efficacy and safety of apremilast (CC-10004), in subjects with moderate plaque psoriasis. Identifier: NCT02555826. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2015. Available from https://clinicaltrials.gov/show/NCT02555826. [406] Additional documents: [407-410]
Van de Kerkhof et al 2008	van de Kerkhof PCM, Segaert S, Lahfa M, Luger TA, Karolyi Z, Kaszuba A, et al. Once weekly administration of etanercept 50mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. Br J Dermatol. 2008;159(5):1177-85. [411] Additional documents: [412]
VOYAGE 1 NCT02207231	Blauvelt A, Papp KA, Griffiths CEM, Randazzo B, Wasfi Y, Shen Y-K, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017;76(3):405-17. [413] Additional documents: [414-426]
VOYAGE 2 NCT02207244	Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. Journal of the American Academy of Dermatology. 2017;76(3):418-31.[427] Additional documents: [415,416,423,424,428,429]
X-PLORE NCT01483599	Gordon KB, Duffin KC, Bissonnette R, Prinz JC, Wasfi Y, Li S, et al. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. N Engl J Med. 2015;373(2):136-44. [430] Additional documents: [431-434]
Zhang et al 2015	Cai L, Gu J, Zheng J, Zheng M, Wang G, Xi LY, et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. J Eur Acad Dermatol Venereol. 2017;31(1):89-95. [435] Additional documents: [436-438]

References for Question C2

- Erratum to: Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial (Br J Dermatol, (2015), 173, 930-939). Br J Dermatol. 2016;174(6):1426. (Provided in original submission reference pack)
- Thaci D et al. Treatment with tildrakizumab, an anti-IL-23p19 monoclonal antibody, improves health-related quality of life in patients with chronic plaque psoriasis. *Ann Rheum Dis*. 2016;75:597. (Provided with this response)
- Langley RGB et al. MK-3222, an anti-IL-23p19 humanized monoclonal antibody, provides significant improvement in psoriasis over 52 weeks of treatment that is maintained after discontinuation of dosing. *J Am Acad Dermatol*. 2014;70(Suppl 1):AB176. (Provided with this response)
- Merck Sharp & Dohme Corp. A study to determine the optimal dose of tildrakizumab (SCH 900222/MK-3222) for the treatment of moderate-to-severe chronic plaque psoriasis (P05495) (MK-3222-003). Identifier: NCT01225731. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2010. Available from https://ClinicalTrials.gov/show/NCT01225731. (Link to reference included)
- Schering-Plough Research Institute. Dose range finding study of subcutaneous SCH900222. Identifier: EUCTR2009-017272-24-DE. In: EU Clinical Trials Register [internet]. London: European Medicines Agency: 2010. Available from https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-017272-24. (Link to reference included)

Summary of additional references and files provided with this response

References

Question Number	Reference file name
A1	ID1060_ERG_clarification questions_CSR for Phase IIb study_AIC.pdf ID1060_ERG_clarification questions_CSR for Phase IIb study_A_AIC.pdf
A2	ID1060_ERG_clarification questions_P010-protocol_original_AIC.pdf ID1060_ERG_clarification questions_Part2_Protocol p010_to_p3501_AIC.pdf ID1060_ERG_clarification questions_Part3_Protocol p010_to_p6932_AIC.pdf ID1060_ERG_clarification questions_Part4_p010_from_p6933_AIC.pdf ID1060_ERG_clarification questions_P011-protocol-original_AIC.pdf
A3	ID1060_ERG clarification questions_Almirall data on file for question A3_AIC.docx
A11	Robinson 2012 J Am Acad Dermatol.pdf
A13	Chaudhari et al 2001 Lancet.pdf Gottlieb et al 2004 J Am Acad Dermatol.pdf Menter et al 2007 J Am Acad Dermatol.pdf Reich et al 2005 Lancet.pdf Torii et al 2010 J Dermatol Sci.pdf Yang et al 2012 Chin Med J.pdf
B2	Sherif et al 2017 Value in Health.pdf
C2	Langley et al 2014 J Am Acad Dermatol.pdf Thaci et al 2016 Ann Rheum Dis.pdf

Text files and Excel spreadsheets

Question Number	Reference file name
A12	FE_weeks1216_placeboAdj.txt RE_weeks1216_placeboAdj.txt placAdj_parameters_convergence.xlsx placebo_response_summary.xlsx placeboAdj_treatment-effects.xlsx PlaceboAdFixed2.xlsx PlaceboAdjRandom2.xlsx
A13 Excluding Phase 2 studies	FE_noP2_noPlacAdj.txt FE_noP2_PlacAdj.txt RE_noP2_noPlacAdj.txt RE_noP2_ placAdj.txt NoP2_noPlacAdj_Random.xlsx NoP2_treatment_effects.xlsx NoP2_parameters_convergence.xlsx NoP2_placAdj_Fixed.xlsx NoP2_noPlacAdj_Fixed.xlsx NoP2_placAdj_Random.xlsx
A13 Excluding unlicenced treatments	FE_licensed_noPlacAdj.txt FE_licensed_PlacAdj.txt RE_licensed_noPlacAdj.txt RE_licensed_placAdj.txt Licensed_treatment_effect.xlsx Licensed_parameters_convergence.xlsx Licensed_noPlacAdj_Fixed.xlsx Licensed_placAdj_Fixed.xlsx Licensed_noPlacAdj_Random.xlsx Licensed_placAdj_Random.xlsx
A13 Including infliximab	FE_infl_stage1_placAdj.txt FE_infl_stage1_noPlacAdj.txt RE_infl_stage1_noPlacAdj.txt RE_infl_stage1_placAdj.txt Infliximab_stage1_placAdj_Fixed.xlsx Infliximab_stage1_noPlacAdj_Fixed.xlsx

	Infliximab_stage1_PlacAdj_Random.xlsx Infliximab_stage1_noPlacAdj_Random.xlsx Infliximab_stage1_treatment_effects.xlsx Infliximab_stage1_parameters_convergence.xlsx Additional infliximab data used in sensitivity analysis.docx Relative risks_infliximab_comparators.docx
A13 Additional analysis 1	Addition sens anal 1 infliximab licensed.docx FE_infl_licensed_noPlacAdj.txt FE_infl_licensed_PlacAdj.txt RE_infl_licesned_noPlacAdj.txt RE_infl_licensed_PlacAdj.txt Infliximab_licensed_noPlacAdj_Fixed.xlsx Infliximab_licensed_noPlacAdj_Random.xlsx Infliximab_licensed_parameters_convergence.xlsx Infliximab_licensed_PlacAdj_Fixed.xlsx Infliximab_licensed_PlacAdj_Random.xlsx Infliximab_licensed_treatment_effects.xlsx
A13 Addional analysis 2	Addition sens anal 2 infliximab stage 3.docx FE_infl_stage 3_noPlacAdj.txt FE_infl_stage 3_PlacAdj.txt RE_infl_stage 3_noPlacAdj.txt RE_infl_stage 3_PlacAdj.txt Infliximab_stage 3_noPlacAdj_Fixed.xlsx Infliximab_stage 3_noPlacAdj_Random.xlsx Infliximab_stage 3_parameters_convergence.xlsx Infliximab_stage 3_PlacAdj_Fixed.xlsx Infliximab_stage 3_PlacAdj_Random.xlsx Infliximab_stage 3_treatment_effects.xlsx
A15	Q15 direct and indirect data_w28.xlsx
Economic models (2 versions are included)	ID1060_HE model_clarfication questions_v1_AIC This version of the HE model is set up using utility by PASI score updated using EQ-5D UK value set for all patients. Relative risks at 14 weeks have been added for infliximab based on the latest NMA. The RRs for all other comparators are based on the original network. ID1060_HE model_clarfication questions_v2_AIC This version of the economic model is set up using utility by PASI score updated using EQ-5D UK value set for all patients AND

	relative risks at 14 weeks updated for all comparators based on the latest network that includes infliximab.

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis Association
3. Job title or position	Chief Executive
4a. Brief description of the organisation (including who funds it). How many members does it have?	Patient Support Organisation and Charity. The Psoriasis Association currently has around 2300 members who help to fund the organisation via an annual fee. Other sources of income include fundraising (individuals, legacies and trusts), investments and unrestricted educational grants from the Pharmaceutical Industry for projects (there is a policy that no more than 15% of the total income of the Psoriasis Association can come from the Pharmaceutical Industry). In addition to traditional members, the Psoriasis Association regularly communicates with, or offers a platform enabling people whose lives are affected by the condition to communicate with one another via online forums on their own websites (8,000 registered users), and Social Media (15,000 people). The main Psoriasis Association website averages 45, 000 visits per month.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the	This submission has been informed by informal, anecdotal information that we hear from patients and carers themselves, through the following channels provided by the Psoriasis Association:-

experiences of patients and carers to include in your submission?	the Psoriasis Association website (566,961 visitors in 2017) telephone helpline (850 enquiries in 2017) online forums (8,490 registered users in 2017) social media channels (including Facebook Group, Twitter and Instagram, 15,000 people in 2017)
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Psoriasis is a lifelong condition with varying degrees of severity. The patients for whom this treatment is intended, those with moderate to severe disease, will have a degree of psoriasis that will not only be visible to others, but also be itchy, painful and produce excess scales. The scales are unsightly, and can cause problems with employment and work colleagues in many industries. Owing to the highly visible nature of psoriasis, and its unsightliness, patients can often adopt negative coping mechanisms such as avoiding social situations (in the hope of avoiding negative reactions from members of the general public). This can mean that the condition itself is isolating and lonely. This can in turn lead to adopting unhealthy lifestyle choices, such as alcohol and drug use, lack of exercise and smoking. Patients with moderate to severe psoriasis have usually been through a long journey of treatment trial and error and expense. When psoriasis is first diagnosed, patients will usually be prescribed topical treatments (creams and ointments). Our latest membership survey found that people were spending on average two hours every day treating their (mild) psoriasis. This involves regularly moisturising the skin (essential in order to keep the skin comfortable, to help with itch and to reduce flakes from falling – having

	to share a desk at work can be very difficult for people with psoriasis), and applying creams and ointments with more active ingredients. The majority of respondents in our membership survey reported psoriasis impacting on their choice of clothing, from regularly "covering up" in the summer months in long sleeves and long trousers, to the colour of clothing on the top half of the body (men report frequently having light suits for work to help conceal the shedding of scales, whilst women consciously sought certain fabrics so as not to have clothing ruined by treatments). It is often unsustainable to treat psoriasis with topical treatments alone, and patients will need more help to cope with a flare, or to maintain the condition at a manageable level. The traditional next stage has been Ultraviolet Light Therapy, but for some patients this form of treatment is not considered owing to the time commitment required (attending the Dermatology Department three times per week for 10 weeks). Traditional systemic treatments for psoriasis would then be considered if the psoriasis was deemed to be moderate to severe in nature. It is vitally important however to measure, record and treat not only the physical symptoms of psoriasis, but the psychological impact the condition can have. Being a lifelong condition, the psychological impact may not initially be realised, which is why it is important for this assessment to be made over the course of the disease. Psoriasis in high impact areas such as the hands, feet, face or genitals is not only a problem for people owing to the visibility of the condition. Deep cracks to the fingertips (not to mention nail psoriasis) can be disabling for those whose trade requires use of the hands and fingers (e.g. musicians, artists, mechanics, not to forget general office-based administration roles). Psoriasis on the feet can make walking difficult, even wearing shoes. Psoriasis on the face can be especially distressing, and we know people avoid

	intimate relationships so as not to have to expose genital psoriasis. For those in steady relationships, sexual relationships can be difficult owing to the pain experienced by genital psoriasis. People report deliberately not having children in case they too develop psoriasis. For those with moderate – severe psoriasis who do want children, their choice of treatment is limited owing to the teratogenicity of traditional systemic medications. Psoriasis therefore can affect every stage of life to varying degrees – from bullying in school, through to difficulty writing in exams, choice of career, having children, holidays and long-term relationships. Access to treatments that are appropriate, suitable and reliable is vital.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There has long been a frustration amongst those with clinically moderate psoriasis that their psoriasis is not "bad enough" to warrant systemic, or newer biological therapies, yet it is too severe to manage with topical treatments alone. This patient population are stuck in limbo. Sadly there is a postcode lottery in terms of care available on the NHS, for some, usually those who have been in the system for a while, it is good. For many there is little access to secondary care (where drugs for moderate to severe psoriasis are prescribed) as lists are closed or extremely lengthy or GPs are unwilling / unable to refer. A recent caller to the Psoriasis Association with schizophrenia in addition to moderate – severe psoriasis, said that living with schizophrenia was made easier than living with psoriasis as he could access specialist services more readily. He questioned why it had taken 12 years for him to be referred to see a Dermatologist.
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	It is a highly targeted treatment for psoriasis, moving away from the blanket immune suppression of traditional systemic treatments for psoriasis. Tildrakizumab is an IL-23 blocking agent, of which there is currently just one other option available for people with psoriasis (there are a number of anti-TNF and IL-17 blockers available). Therefore, it is an advantage to have an alternative agent working on this pathway. The twelve-weekly dosing regimen is very appealing to patients as it is minimally invasive to everyday life.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The fact that it is an injection will always concern a cohort of patients.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those for whom other treatments have failed – many people with moderate to severe psoriasis will eventually lose efficacy from biologic treatments and, as psoriasis is a lifelong condition, it is essential to have new options for this cohort to move on to.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The PASI is not a suitable assessment for psoriasis on high impact sites (such as the hands, feet, face and genitals). It is also not as robust a measure in black skin.
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Psoriasis is a lifelong condition in which individuals respond differently to different treatments. For this reason a range of treatment options for all degrees of severity is required.
- There is currently unmet need in the treatment of people with moderate psoriasis (for whom topical treatments nor biologics are suitable).

- High impact sites such as the face, hands, feet and genitals should not be overlooked when defining treatment criteria (these sites will not produce a high PASI score).
- Itch should be considered as a treatment outcome.
- This technology adds a useful new option for those who have failed all other available treatments. Psoriasis is a lifelong condition and therefore new treatment options are always needed for those who lose efficacy on existing treatments.

Thank you for your time.

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Patient organisation submission

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

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
3. Job title or position	Chief executive
4a. Brief description of the organisation (including who funds it). How many members does it have?	PAPAA is a national charity, which provides information and support to people affected by psoriasis and psoriatic arthritis. The current incarnation followed the merger of two separate organisations, with the oldest dating back to 1992. Although the charity has no formal membership, it has a supporter register of >13,000 people which includes both patients and healthcare professionals. In a changing 21st century, activity and support has evolved with more taking place online, with most interaction via that medium. The main charity website had >800,000 page views during the past year. Regular use of feedback forms and online surveys help to direct the charity's work and how it represents its constituent group. Funding is via donations, subscriptions and from the sale of promotional items. Financial support is not accepted from the pharmaceutical industry, either as direct payment or in-kind, this includes third-party work via PR or research agencies. The organisation values its independence and feels this provides an agenda which is patient-centred and not driven by marketing or promotional activities that may be behind such support, however arms-length or segmented.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	Data for this submission has been gathered via our online surveys and direct feedback. We compile ongoing views and opinions of those who interact with us to provide a broad consensus that we think reflects the general psoriasis population that is likely to be those who would potentially qualify for tildrakizumab.

carers to include inyour submission?	
Living with the condition	
6. What is it like to live with the condition?What do carers experience when caring for someone with the condition?	To live with psoriasis for many people can be just a mild irritation, causing little or no major impact. The severity of psoriasis doesn't always reflect how an individual will feel or manage the condition. This large group of individuals, who manage their condition adequately, hides the fact that for a significant group with uncontrolled chronic disease, find that psoriasis dominates every aspect their life. People become anxious and frustrated of the often poor control of symptoms, which can have a profound effect on their emotional state. They become self-conscious of the look and feel of the skin and the continuous shedding of flakes, particularly on their clothes and surrounding area, which people describe as leaving a "trail of debris". We spoke to an individual via our helpline, who said she took a vacuum cleaner with her when she stayed in a hotel because of the embarrassment her shed skin had on the state of the room overnight. The following are quotes submitted via our online surveys: "Worried for the future. At the moment the side effects from methotrexate are worse than the condition!" "Awful. It's a combination of pain, weakness, deformity, dreadful fatigue and the uncertainty of knowing what each day will bring." "There are also huge psychological issues around "what might have been" as well as appearance in terms of skin problems, deformity and "disabledness" - even from a young age." "Frustrating and embarrassing. I often live in cyclical stress of knowing I could break out and knowing I need to control my stress levels."

	"When at its worst and uncontrolled it was unbearable. I used to get it on the back of my head so as it shed it always looked like dandruff. I had it on my back and worst of all around my backside, which used to get so raw I literally could not walk at all. And I am only in my 30s." "Intrusive. I have found my life has become a lot more insular due to the constant fatigue and attitude towards skin issues." "It's embarrassing & demoralising for me. I have very bad psoriasis on both knees and elbows. I do wear T shirts & short sleeved tops but I ALWAYS have to wear long dresses, trousers or leggings to hide my unsightly knees, otherwise I notice other people staring at my knees. That's not a good feeling." "As a teenager horrendous, suicide attempt, eating disorder, still have issues with body image 30 yrs later. Worst comment received: being told by a passing stranger I should kill myself so people didn't have to look at me, but received unpleasant / embarrassing comments most days from total strangers." "The shame of smelling of coal tar and leaving piles of scales wherever I was sat. Not forgetting the itching, pain, sleepless nights." "Unable to get jobs in anything relating to food/ drink, public facing because of it. First medical to get into nurse training was failed as having psoriasis proves you're mentally incapable of holding a job down (2nd Dr not so antiquated in attitude)." " Has been less severe over last decade, controlled with tight diet that is slightly restricting socially but prefer this to the psoriasis, even ventured back to dermatology (gave up on them as no topical treatments worked and not offered anything else)" "I've had it since I was 13, that horrible self conscious age, when you really want to fit in, I've hated it all the years I've had it, I've had it get that bad that I've considered suicide, as an end to the horrible painful, itchy scales and the looks off people that think you have a contagious disease."

	"Only had symptoms in the last four years, as an adult. Is a struggle to live with. More so when coupled with arthritic symptoms too."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In sections of our survey we ask peoples' views about current therapies the following are direct quotes: "Thankful that there are some treatments but having difficulty dealing with the side effects. Have psychosomatic symptoms." "There appears to be a reasonable range available, but prescribing guidelines do not seem to be uniform nationwide." "They're scary. You trade one disease for many others, including cancer. Who wants that?" "Poor availability. 30+ years of heavy topical steroid use has impacted. Only recently had access to acitretin and methotrexate, which did nothing for me. Had to push very hard to get access to these and only once I was at the point of not being able to carry out day to day activities any more. Currently on ciclosporin which is having a positive impact but clear concern from the specialist over safety." "Scary" "My initial treatments were useless, I used tonnes of creams and useless sulfasalasine, which didn't help." "That depends to whom you speak. I have found the advice/knowledge of the disease varies massively

	between supposed professionals. I always try to go with as much research as possible so I cannot be 'palmed' off with whatever they assume I need." "Nothing works. I have had psoriasis for 27 years and no treatment I have tried has ever worked" "More treatments available, less emphasis for severe disease on the unpleasant topical treatments of 80s/ 90s" "I love etanercept, I've been on it 6 months and I wish I'd of known about it when it first came out!" "I've been on a lot of topical treatments with no success. And also tried newer biologics like ustekinumab and apremilast, with limited success. I am about to start secukinumab".
8. Is there an unmet need for patients with this condition?	Even with the range of newer therapies that have become available recently, there are still people where those fail or there is limited efficacy, which given stopping rules leaves these individuals with progressive disease and little further options. Therefore more choice would provide some hope for the groups who have an unmet need.
Advantages ofthe technology	
9. What do patients or carers think are the advantages of the technology?	We have no information or experience of people using the treatment being appraised. It appears to be similar in delivery to other sub-cutaneous biologic agents with a different target inhibiting the action of interleukin 23, so could be an advantage in those who have had no response to other biologic agents against other targets. The dosage period after initial loading at every 12-weeks might be advantages to people where these less frequent injections allows for travel and easier storage.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Similarly we have no information related to the drug being appraised, so would assume that any disadvantages would be similar to other same class agents. Therefore as with other agents, access due to high cost may delay people moving onto these targeted treatments, or being delayed by having to try other less effective therapies first.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those with psoriatic arthritis could benefit, if it is proven to be effective in that element of the disease too.
Equality	
12. Are there any potential equality issues that should be taken into account when	We don't believe there are any equality issues that need to be considered as set out in law. Although, there are those who have needle phobias and there could be individuals who have arthritic hands which might make self-injection difficult, but provision already exists to help these individuals.

considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission: • Psoriasis is a life-long lonely disease with unpredictable flares and remission • Psoriasis can impact many areas of an individual's life, including relationships. • There is a need for further choice, when other therapies fail. • Psoriatic arthritis could be considered when making therapy choices	

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	British Association of Dermatologists

3. Job title or position	**Consultant Dermatologist; chair of the Therapy & Guidelines sub-committee**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a charity whose charitable objectives are the practice, teaching, training and research of Dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of Dermatology services across all service settings. It is funded by the activities of its Members
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	• Control of psoriasis with the aim of a 'clear' or 'nearly clear' by Physician's Global Assessment rating • Reducing the impact of the disease on quality of life

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Current guidelines (specifically the published 2017 BAD guidelines on biologic therapies for psoriasis, and prior NICE STAs have defined a minimum clinically significant improvement as: • ≥ 50% reduction in baseline disease severity, e.g. a PASI50 response, or percentage BSA where PASI is not applicable, and • Clinically relevant improvement in physical, psychological or social functioning (e.g. ≥ a 4-point improvement in DLQI score or resolution of low mood)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes: 1. In real-world practice, not all people with psoriasis who fulfil NICE criteria for biologic therapy respond to existing biologic therapies; secondary failure is also common (Patterns of biologic therapy use in the management of psoriasis: cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). Br J Dermatol. 2017 May;176(5):1297-1307. doi: 10.1111/bjd.15027. Epub 2017 Mar 20. PubMed PMID:27589476; Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015 Nov;135(11):2632-2640. doi: 10.1038/jid.2015.208. Epub 2015 Jun 8. PubMed PMID:26053050; Differential Drug Survival of Second-

	Line Biologic Therapies in Patients with Psoriasis, J Invest Dermatol. 2018 Apr;138(4):775-784. doi: 10.1016/j.jid.2017.09.044. Epub 2017 Dec 6. **N.B.** Additional reference: Biologics may be less effective in the real world, cf. to trial data due to use of biologic therapies. Comparison of Drug Discontinuation, Effectiveness, and Safety Between Clinical Trial Eligible and Ineligible Patients in BADBIR JAMA Dermatol. 2018 May 1;154(5):581-588. doi: 10.1001/jamadermatol.2018.0183. Use of biologic therapy in the UK is currently limited to those with severe disease as defined by a PASI 10. This excludes use of highly effective biologic therapy including certolizumab pegol (within the licensed indication – i.e. moderate or severe) where the disease is associated with a severe impact on their QoL, physical, social or psychological function. Specifically, people with moderate disease and those with severe disease but of limited extent – i.e. high-need areas such as the face, hands, feet, flexural/genital sites. People in these two groups will not have a PASI score of 10 but nevertheless will suffer major impact from their disease. Options for these patients are profoundly limited if methotrexate is not effective or cannot be tolerated. Newer small molecule drugs (e.g. dimethyl fumarate and apremilast) are not approved by NICE for patients with a PASI <10 either.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	With NICE-approved biologic therapies and biosimilars; apremilast; dimethyl fumarate; standard systemic therapies (see NICE CG153).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes: BAD guideline for biologic therapy for psoriasis http://onlinelibrary.wiley.com/doi/10.1111/bjd.15665/full NICE CG153 www.nice.org.uk/guidance/cg153 Please note the following comments regarding the final scope below ➔ There should be mention of psoriatic arthritis as an important, common co-morbidity and that when present, of the standard systemic therapies used in psoriasis, only methotrexate is helpful for both joints and skin.

	As previously communicated for more recent biologic STAs for psoriasis, the final scope mentions that "most treatments reduce the severity of psoriasis flares rather than prevent episodes" – there is no evidence that any of the treatments are disease-modifying. This would better describe the point being made here (rather than "most treatments reduce the severity….") as many of the new biologic treatments do clear or nearly clear the disease and maintain it in this state.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes – please see NICE CG153. Data from BADBIR national pharmacovigilance registry suggest that most people with psoriasis fulfil stipulated criteria, e.g. PASI mean (SD) = 16.4 (8.3) – please see Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. Br J Dermatol. 2015 Aug;173(2):510-8. doi: 10.1111/bjd.13908. Epub 2015 Jul 6. PubMed PMID:25989336. **N.B.** Clinical re-audit report based on CG153 standards www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-audits/psoriasis/psoriasis-2017 (July 2018)
• What impact would the technology have on the current pathway of care?	An additional option to consider in people with severe psoriasis; an agent with a novel mode of action, i.e. IL23 receptor antagonist. More agents within the same 'market' may provide motivation to drive down the price.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – biologic therapy is a well-established intervention in psoriasis.
• How does healthcare resource use differ	There would not be any expected differences in health resource use compared to existing NICE-approved agents.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment would be required.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	N/A
• Do you expect the technology to increase health-related quality of	Potentially yes, by providing an additional treatment option for this major, chronic debilitating disease.

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Biologic therapy has been available on the NHS for people with moderate-to-severe psoriasis who meet the eligibility criteria.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The published 2017 BAD guidelines recommended biologic therapy for the following people with psoriasis: Offer biologic therapy to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated (see NICE guidelines CG153) and the psoriasis has a large impact on physical, psychological or social functioning (e.g. Dermatology Life Quality Index [DLQI] or Children's DLQI > 10 or clinically relevant depressive or anxiety symptoms) and one or more of the following disease severity criteria apply: • the psoriasis is extensive [defined as body surface area (BSA) > 10% or Psoriasis Area and Severity Index (PASI) ≥ 10] • the psoriasis is severe at localized sites and associated with significant functional impairment and/or high levels of distress (for example nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures and genitals). These criteria do extend to additional (small) subsets of people with psoriasis currently not covered by the NICE criteria for biologic therapy and were introduced due the limitations of the PASI disease severity tool (i.e. it is strongly dependent on body surface area affected, and for some people with localised disease at high-need sites the PASI will not reach 10) and the specific burden (and limited options) for people with disease in both compartments (skin and joint). Generally, therapy is stopped when: • the minimal response criteria are not met, either initially or further down the line (i.e. secondary failure) • adverse effects arise, e.g. development of neurological symptoms suggestive of demyelinating disease, or new/worsening pre-existing heart failure

	• the risks outweigh the benefits in a) pregnant females or females planning conception and b) people undergoing elective surgery • live vaccines need to be administered No additional testing from what is already recommended for biologics.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes: The calculation of the QALY does not encompass time off work, costs of emollients and other health care products bought by the patients, or other limitations that psoriasis imposes (e.g. social isolation, avoidance of relationships, stigma, depression, anxiety) or the (often significant) impact it has on family and carers. Further, comorbidities common in psoriasis (psoriatic arthritis, metabolic syndrome, cardiovascular disease) may not be appropriated to the psoriasis. The preferred QoL measure for psoriasis at present is the DLQI, and whilst it is important as it covers domains not specifically captured by EQ5D, it doesn't capture anxiety and depression (which are common in psoriasis). Thus, if the QALYs have been derived using DLQI then it may underestimate the impact; further, we know that the mapping algorithms are not necessarily accurate and so the accuracy of the QALY calculation will depend on the algorithm. A new tool based on real world data is now available (Generating EQ-5D-3L Utility Scores from the Dermatology Life Quality Index: A Mapping Studying Patients with Psoriasis, Value in Health, article in press DOI: https://doi.org/10.1016/j.jval.2017.10.024).
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	Targeting the IL-23 pathway is a new treatment approach psoriasis and mAb directed against the IL23 p19 sub-unit (including tildrakizumab) appear to be highly effective, particularly with respect to achieving disease clearance. The dosing schedule of tildrakizumab (every 12 weeks) maybe helpful / preferred by some individuals (cf to guselkumab).

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Antagonism of the IL23 pathway represent a step-change in the management of people with moderate-to-severe psoriasis
• Does the use of the technology address any particular unmet need of the patient population?	Please see response in Q8 above.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Tildrakizumab seems to have a comparable safety profile with other biologic therapies, although there is currently little data about its safety in a real-world population.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	**The following outcomes were reported in the trials:** PASI90, PASI75, PGA 0/1, DLQI, serious AEs. All these outcomes are important and relevant. Other outcomes that may not have been reported but are highly relevant include: • **Psoriasis improvement on the face, scalp, nails:** Plus, other high-need sites, i.e. hands and feet, flexural/genital psoriasis. • **Response rate:** Over what time period? It would be important to include longer treatment outcomes, i.e. 1 year, 2 years. • **Relapse rate:** over what time period? It would be important to include longer treatment outcomes, i.e. 1 year, 2 years. • **Adverse effects of treatment:** infection; separate out adverse effects in the very short term, e.g. during loading doses. • **Health-related quality of life (including dermatology quality of life index [DLQI]):** Include other measures of impact, i.e. depression, anxiety; and impact on psoriatic arthritis.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	See notes above.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There is very limited information about use of the technology outside clinical trials. It would be extremely important for all people with psoriasis who meet the eligibility criteria to be enrolled in BADBIR when prescribed this agent to ensure capture of high quality pharmacovigilance data and to allow relevant comparisons with other biologic agents (N.B. > 16,000 patients now registered – please see www.badbir.org.uk)
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No; however, ciclosporin cannot be used for > 1 year and is therefore not a relevant comparator for this STA. Similarly, PUVA is associated with increased risk of skin cancer and can only be used in the shorter term.

21. How do data on real-world experience compare with the trial data?	Not yet available for this technology.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The PASI may underestimate disease severity in people with darker skin (type IV-VI) as redness may be less evidence (a key component of the PASI). DLQI will underestimate the impact in people who are not sexually active, or older (retired) or socially isolated; it does not capture anxiety and depression.
22b. Consider whether these issues are different from issues with current care and why.	These are generic issues.
Key messages	
24. In up to 5 bullet points, please summarise the key messages of your submission. • Important new technology • High efficacy rates, especially in relation to disease clearance • Existing therapies, while effective for many, do not work for *all* those requiring treatment • NICE criteria for biologic therapy – if applied here – limit access for people who would benefit (not just applicable to this technology)	

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Jonathan Barker**
2. Name of organisation	**KCL and GSTFT**

3. Job title or position	**Professor of Medical Dermatology and honorary consultant dermatologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? X☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	X☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reverse the clinical signs of the disease and hence reduce disfigurement and related outcomes
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in PASI by >75%
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	YES
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Biologics are reserved for patients with difficult ton treat severe disease
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes NICE and BAD
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Fairly well defined but there is variation across England
• What impact would the technology have on the current pathway of care?	Increase therapeutic opportunity
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	YES

• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nothing above what already exists
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	YES
• Do you expect the technology to increase length of life more than current care?	Psoriasis is a chronic disabling disease

• Do you expect the technology to increase health-related quality of life more than current care?	Yes for some patients
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with difficult to treat severe psoriasis
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	No

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	YES
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I don't know enough about how QALY calculated to comment
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	YES

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	Long term efficacy
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Profile is similar to current therapies
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes to some extent
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as “Is comparator X [excluded from company submission] considered to be established clinical practice in	

the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • Despite great advances severe psoriasis management remains challenging • Long term safe control remains key goal • It is very helpful to have more than one drug in any class • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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

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Declared competing interests of the authors

None.

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Rider on responsibility for report

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

This report should be referenced as follows: Walker R, Fusco F, Carlson J, Corbett M, Wright K, Woolacott N, Palmer S. Tildrakizumab for treating moderate to severe plaque psoriasis: A Single Technology Appraisal. CRD and CHE, University of York, Technology Assessment Group, 2018

Contributions of authors

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

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined

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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

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

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.

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.

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]

[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.

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.

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

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.

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.

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

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

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.

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.

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.

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.

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

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.

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

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).

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]

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.

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?

- 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.

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.

Trial design

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

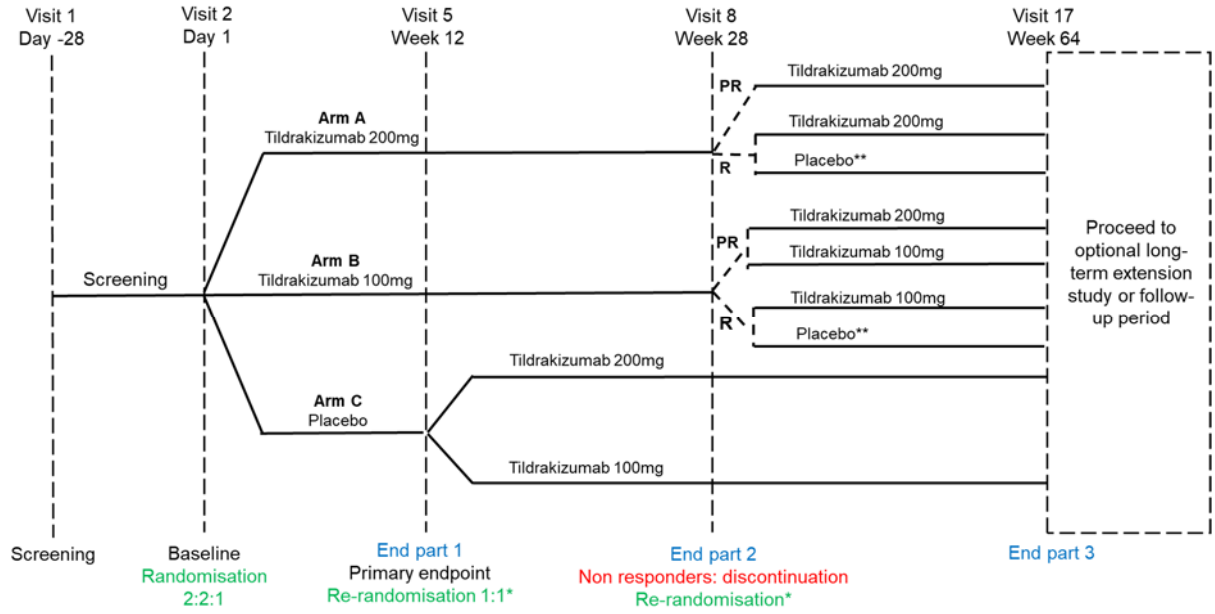


Figure 1 reSURFACE 1 study design (CS Figure 5, page 26 CS)

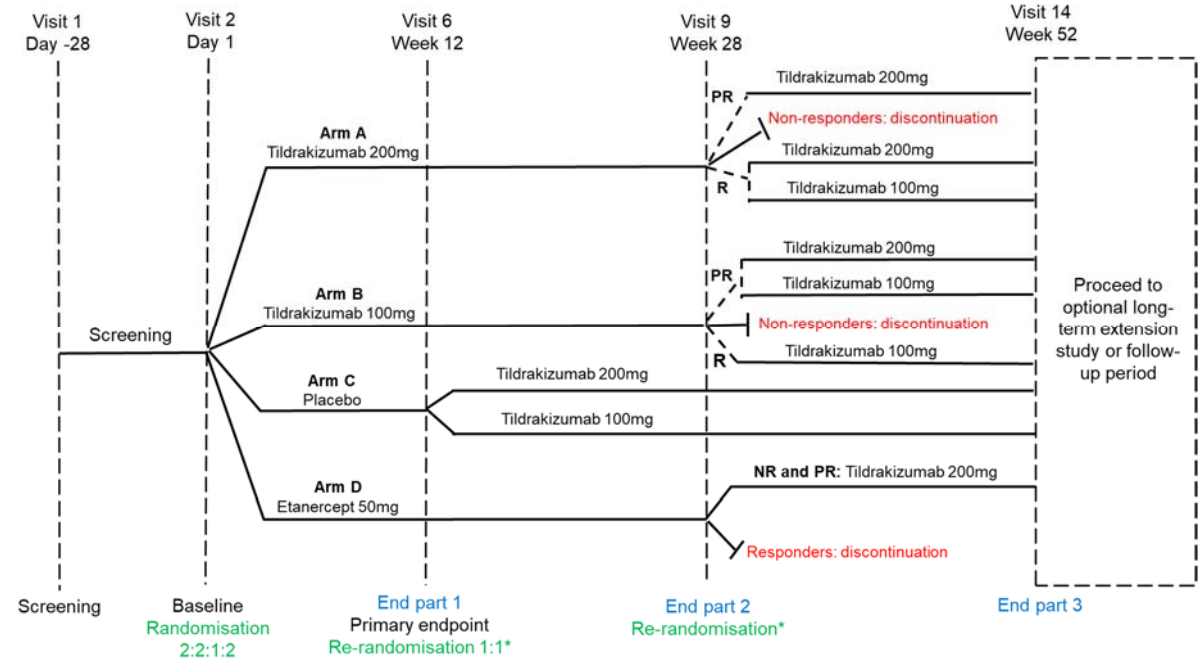


Figure 2 reSURFACE2 study design (CS Figure 6, page 27 of the CS)

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

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.

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

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]

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

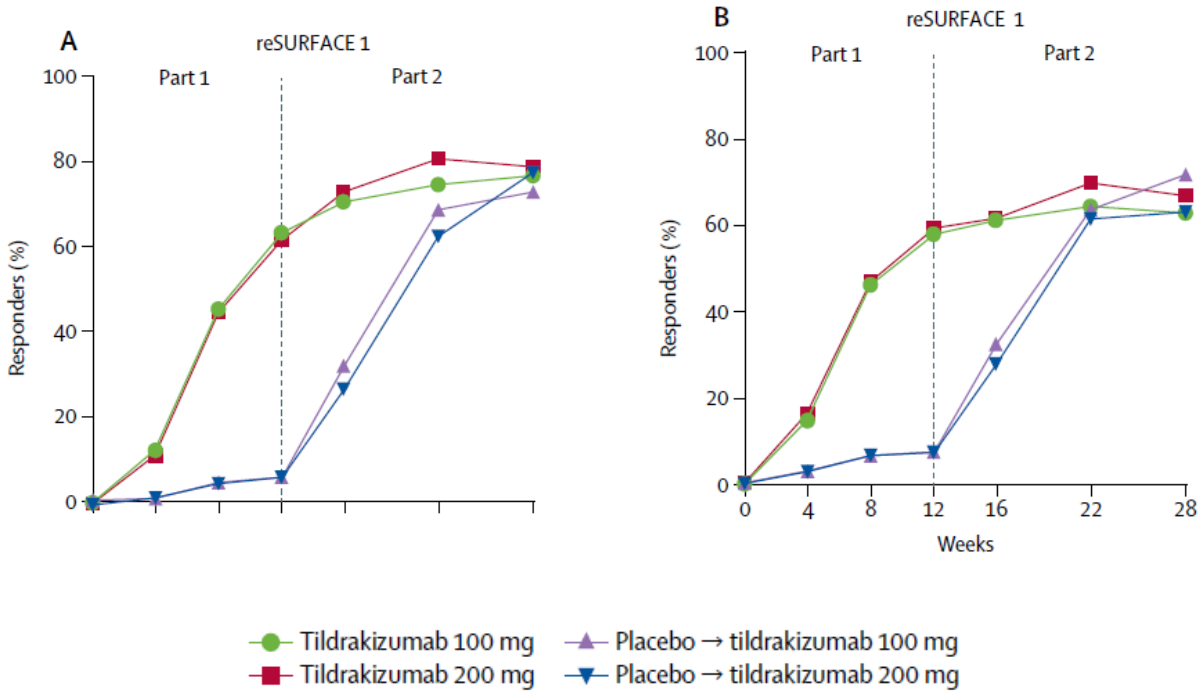
Clinical efficacy data for reSURFACE1 are presented in section B.2.6 of the CS. These efficacy data are based on the FAS with non-responder imputation (as most appropriate) and are summarised along with the quality of life measure DLQI and EQ5D in Table 3. The outcome EQ5D, whilst not being a key primary 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.

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).



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

(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

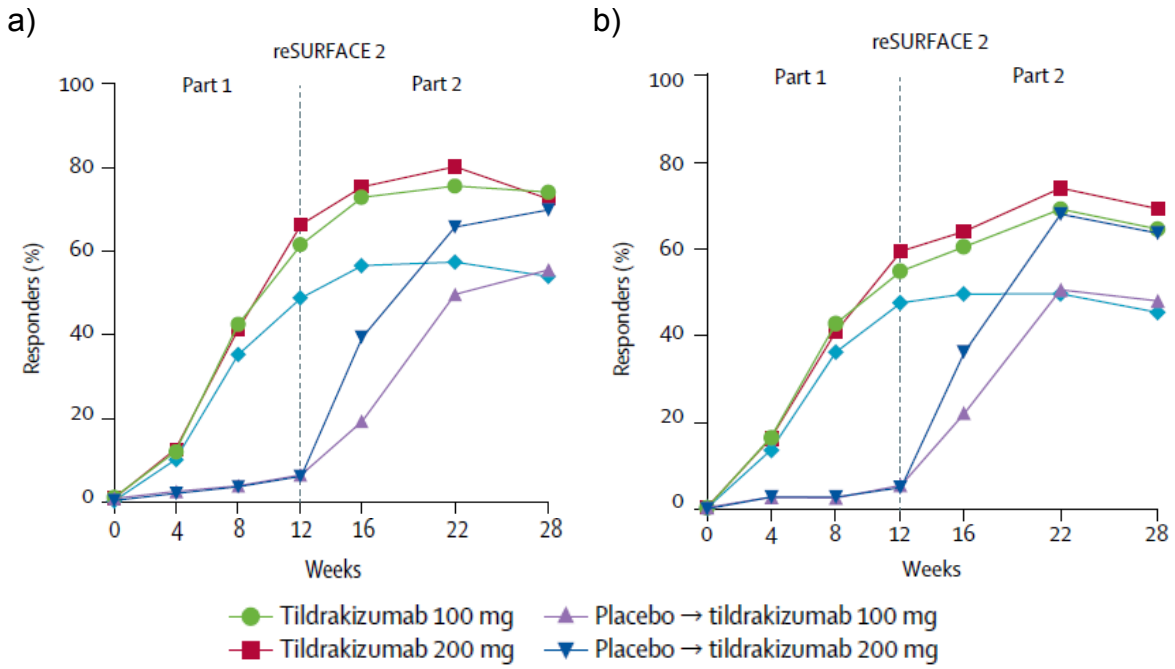
placebo at 12 weeks and better than etanercept at 12 weeks and 28 weeks. Tildrakizumab 100mg performed statistically significantly better than placebo at 12 weeks but not etanercept and at 28 weeks tildrakizumab 100mg performed statistically significantly better than etanercept.

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.

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]

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

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]

[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]

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)

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.

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

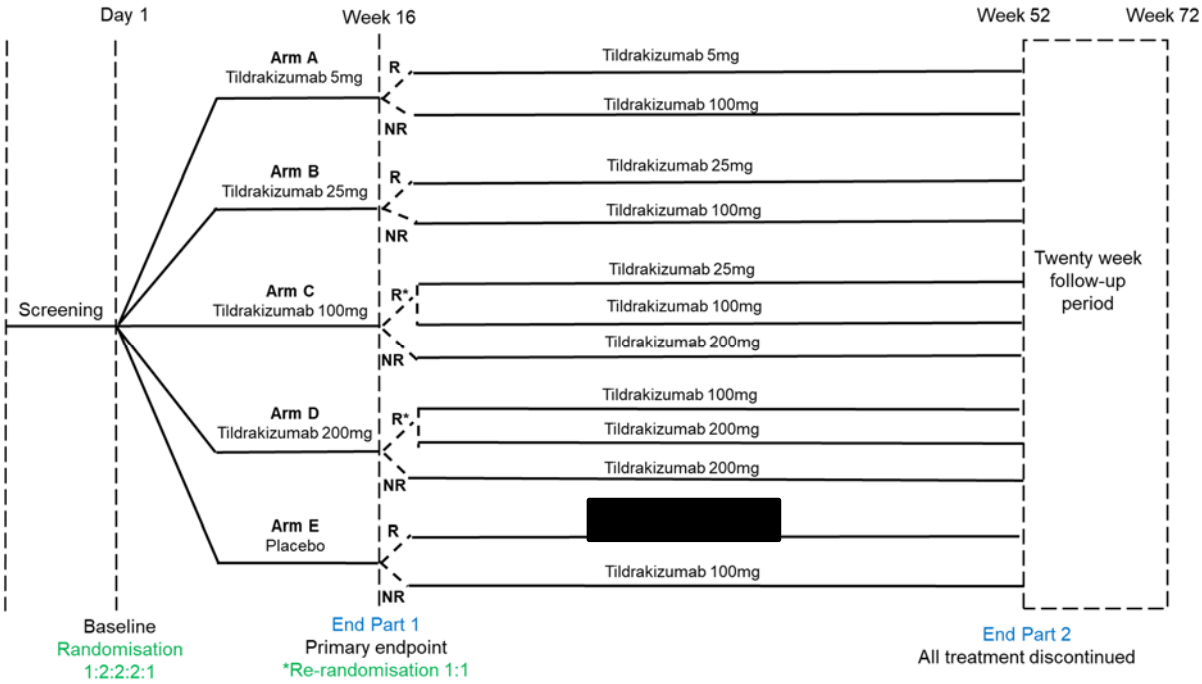
The phase IIb, randomised, double-blind, placebo-controlled trial [7] was conducted to evaluate the safety and efficacy of subcutaneous tildrakizumab in patients with moderate-to-severe chronic plaque psoriasis. The details are summarised in Table 8. In contrast to the phase III trials the primary time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

	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

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).

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 an was carried forward for any subject who missed the end point assessr and who had not discontinued treatment owing to lack of efficacy, lo 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.

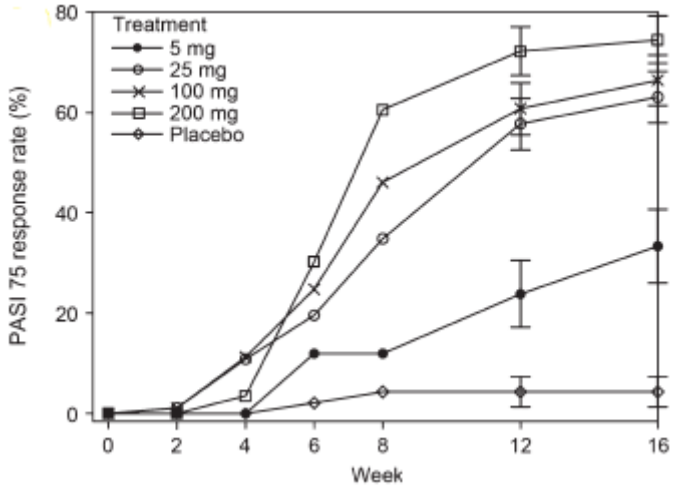


Figure 7 Psoriasis area and severity index (PASI) 75 over time during the placebo-controlled phase 1 (Weeks 0-16). Adapted from Papp et al. 2015.

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

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

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

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 .

- 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:

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

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

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

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'

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

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:

- 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.

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.

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).

Table 14 Redacted

Figure 8 Redacted

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.

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]

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	[redacted]										
12/16 week data (RE, npa)	[redacted]										
PASI100 Vs Placebo	[redacted]										
24/28 week data (RE, npa)	[redacted]										

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]

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.

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.

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

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.

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

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

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)

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)

		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)

		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-)

5.2.1 NICE reference case checklist

The NICE reference case checklist is given in Table 18.

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	

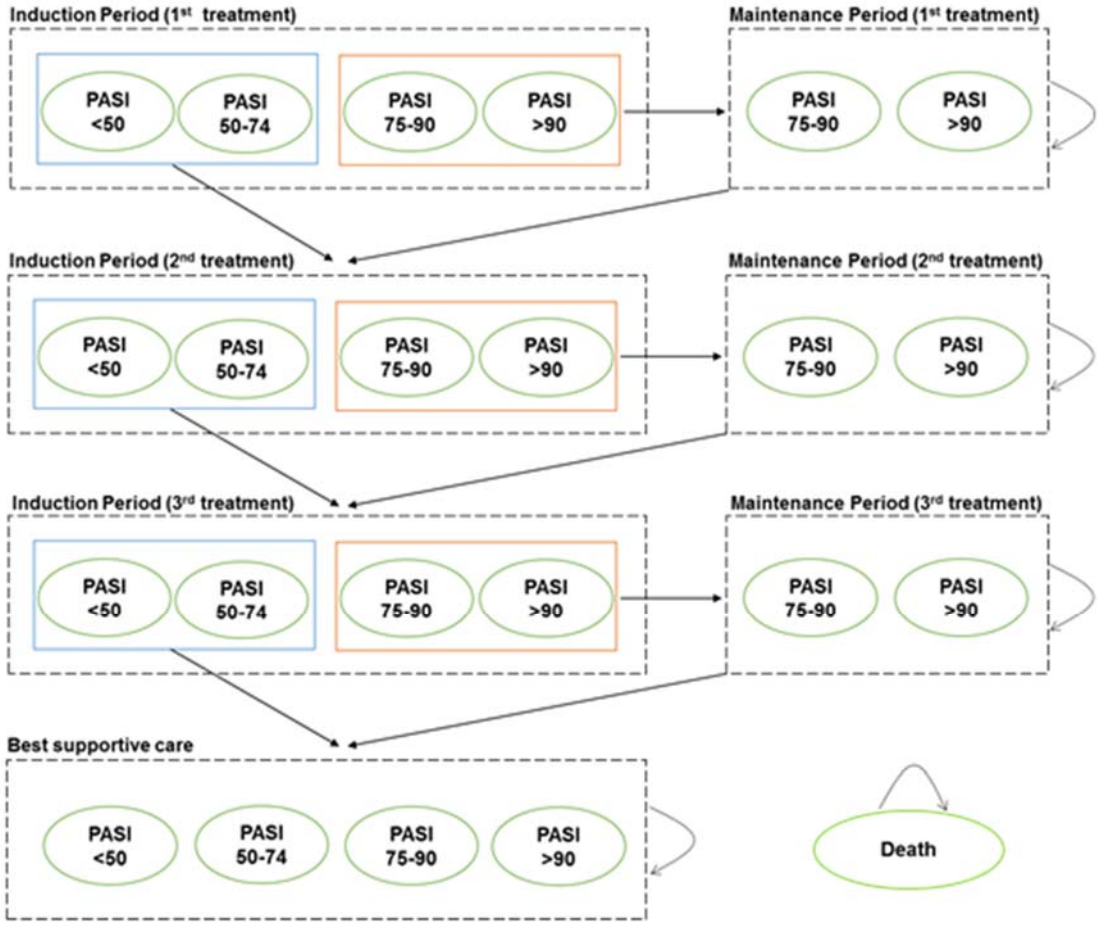
Element of economic evaluation	NICE Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes	
Time horizon	Long enough to reflect all important differences 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.

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	

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

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.

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

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

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.

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]

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).

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

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

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.

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)

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

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

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

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

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

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]

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

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.

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.

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.

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

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.

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

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

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]

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.

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.

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.

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.

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

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.

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

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.

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

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

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.

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.

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

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.

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.

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.

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.

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).

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.

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

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.

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:

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*.

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

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

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.

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

- 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.

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

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.

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

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.

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

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

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.

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

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.

			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) The different approaches to dealing with sequences

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) The different assumptions for the cost of BSC

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

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 ([redacted]) is not used in the model. Instead, the minimum utility estimate applied in the model is [redacted] (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 = [redacted]], PASI 50-74 [utility value = [redacted]], PASI 75-89 [utility value = [redacted]], PASI ≥90 [utility value = [redacted]]) informed from the NMA. The second approach assumes that the utility value of people receiving BSC alone is the same as the baseline utility ([redacted]).

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

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

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

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.

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

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

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.

7 End of life

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

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.

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.

9 References

1. Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, *et al.* European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009;**23 Suppl 2**:1-70. 10.1111/j.1468-3083.2009.03389.x

2. Parisi R, Symmons D, Griffiths C, Ashcroft D, Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* 2013;**133**:377-85.

3. Springate D, Parisi R, Kontopantelis E, Reeves D, Griffiths C, Ashcroft D. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. *Br J Dermatol* 2017;**176**:650-8.

4. National Institute for Health and Care Excellence. *Psoriasis: assessment and management*. 2017. URL: https://www.nice.org.uk/guidance/cg153 (accessed 13th November 2017).

5. Reich K, Papp KA, Blauvelt A, Tyring SK, Sinclair R, Thaçi D, *et al.* Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet* 2017;**390**:276-88. 10.1016/s0140-6736(17)31279-5

6. Iskandar IY, Ashcroft DM, Warren RB, Yiu ZZ, McElhone K, Lunt M, *et al.* Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. *Br J Dermatol* 2015;**173**:510-8. 10.1111/bjd.13908

7. Papp K, Thaci D, Reich K, Riedl E, Langley RG, Krueger JG, *et al.* Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol* 2015;**173**:930-9. 10.1111/bjd.13932

8. Warren RB, Smith CH, Yiu ZZN, Ashcroft DM, Barker J, Burden AD, *et al.* Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol* 2015;**135**:2632-40. S0022-202X(15)41849-4 [pii]

10.1038/jid.2015.208

9. Egeberg A, Ottosen MB, Gniadecki R, Broesby-Olsen S, Dam TN, Bryld LE, *et al.* Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. *Br J Dermatol* 2018;**178**:509-19. 10.1111/bjd.16102

10. Blauvelt A, Reich K, Papp KA, Kimball AB, Gooderham M, Tyring SK, *et al.* Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials. *Br J Dermatol* 2018. 10.1111/bjd.16724

11. Liu GF, Wang J, Liu K, Snavely DB. Confidence intervals for an exposure adjusted incidence rate difference with applications to clinical trials. *Stat Med* 2006;**25**:1275-86.

12. Institute for Clinical and Economic Review. *Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value. Condition Update. Draft Evidence Report*. Boston, MA: ICER; 2018.

13. Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. *Br J Dermatol* 2011;**165**:661-8. 10.1111/j.1365-2133.2011.10419.x

14. Gottlieb AB, Leonardi C, Kerdel F, Mehlis S, Olds M, Williams DA. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. *Br J Dermatol* 2011;**165**:652-60. 10.1111/j.1365-2133.2011.10418.x

15. Bachelez H, van de Kerkhof PCM, Strohal R, Kubanov A, Valenzuela F, Lee J-H*, et al.* Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. *Lancet* 2015;**386**:552-61. 10.1016/s0140-6736(14)62113-9

16. de Vries AC, Thio HB, de Kort WJ, Opmeer BC, van der Stok HM, de Jong EM*, et al.* A prospective randomized controlled trial comparing infliximab and etanercept in patients with moderate-to-severe chronic plaque-type psoriasis: the Psoriasis Infliximab vs. Etanercept Comparison Evaluation (PIECE) study. *Br J Dermatol* 2017;**176**:624-33. 10.1111/bjd.14867

17. Blauvelt A, Papp K, Gooderham M. Efficacy and safety of risankizumab, an IL-23 inhibitor, in patients with moderate-to-severe chronic plaque psoriasis: 16-week results from the phase 3 IMMhance trial. Paper presented at: Psoriasis: from gene to clinic; London, UK.

18. Bagel J, Lynde C, Tyring S, Kricorian G, Shi Y, Klekotka P. Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind, placebo-controlled study of etanercept. *J Am Acad Dermatol* 2012;**67**:86-92. S0190-9622(11)00832-2 [pii]

10.1016/j.jaad.2011.07.034

19. Reich K, Pinter A, Lacour JP, Ferrandiz C, Micali G, French LE*, et al.* Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *Br J Dermatol* 2017;**177**:1014-23. 10.1111/bjd.15666

20. Barker J, Hoffmann M, Wozel G, Ortonne JP, Zheng H, van Hoogstraten H*, et al.* Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). *Br J Dermatol* 2011;**165**:1109-17. 10.1111/j.1365-2133.2011.10615.x

21. Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. *J Dermatol Sci* 2010;**59**:40-9. S0923-1811(10)00135-0 [pii]

10.1016/j.jdermsci.2010.04.014

22. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C*, et al.* A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2007;**56**:31 e1-15. S0190-9622(06)02083-4 [pii]

10.1016/j.jaad.2006.07.017

23. Gottlieb AB, Evans R, Li S, SDooley LT, Guzzo CA, D B*, et al.* Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind placebo-controlled trial. *Journal of Academic Dermatology* 2004;**51**:534-42.

24. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet* 2001;**357**:1842-7. 10.1016/s0140-6736(00)04954-0

25. Reich K, Nestle F, Papp K, Ortonne J, Evans R, Guzzo C*, et al.* Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III multicentre double-blind trial. *Lancet* 2005;**366**:1367-74.

26. Yang H-Z, Wang K, Jin H-Z, Gao T-W, Xiao S-X, Xu J-H*, et al.* Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-

controlled multicenter trial. *Chin Med J* 2012;**125**:1845-51. 10.3760/cma.j.issn.0366-6999.2012.11.001

27. Mrowietz U, Leonardi CL, Girolomoni G, Toth D, Morita A, Balki SA*, et al.* Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: A randomized, double-blind, noninferiority trial (SCULPTURE). *J Am Acad Dermatol* 2015;**73**:27-36 e1. S0190-9622(15)01513-3 [pii]

10.1016/j.jaad.2015.04.011

28. Strohal R, Puig L, Chouela E, Tsai TF, Melin J, Freundlich B*, et al.* The efficacy and safety of etanercept when used with as-needed adjunctive topical therapy in a randomised, double-blind study in subjects with moderate-to-severe psoriasis (the PRISTINE trial). *J Dermatolog Treat* 2013;**24**:169-78. 10.3109/09546634.2012.658015

29. Caproni M, Antiga E, Melani L, Volpi W, Del Bianco E, Fabbri P. Serum levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients with psoriasis: a randomized-controlled trial. *J Clin Immunol* 2009;**29**:210-4. 10.1007/s10875-008-9233-0

30. Gisondi P, Del Giglio M, Cotena C, Girolomoni G. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator blinded pilot trial. *Br J Dermatol* 2008;**158**:1345-9.

31. Goldminz AM, Suarez-Farinas M, Wang AC, Dumont N, Krueger JG, Gottlieb AB. CCL20 and IL22 messenger RNA expression after adalimumab vs methotrexate treatment of psoriasis: a randomized clinical trial. *JAMA Dermatology* 2015;**151**:837-46. 2290941 [pii]

10.1001/jamadermatol.2015.0452

32. Papp KA, Kaufmann R, Thaci D, Hu C, Sutherland D, Rohane P. Efficacy and safety of apremilast in subjects with moderate to severe plaque psoriasis: results from a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison study. *Journal of European Academy of Dermatology and Venereology* 2013;**27**:e376-83. 10.1111/j.1468-3083.2012.04716.x

33. Papp K, Leonardi C, Menter A, Ortonne J, Krueger J, Kricorian G*, et al.* Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med* 2012;**366**:1181-9.

34. Robinson A, Kardos M, AB. K. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): Why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. *J Am Acad Dermatol* 2012;**66**:369-75.

35. Dias S, Welton NJ, Sutton AJ, Ades A. *A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Report by the Decision Support Unit*. Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2016.

36. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades A. *Inconsistency in networks of evidence based on randomised controlled trials*. Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2014.

37. Smith CH, Jabbar-Lopez ZK, Yiu ZZ, Bale T, Burden AD, Coates LC*, et al.* British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. *Br J Dermatol* 2017;**177**:628-36. 10.1111/bjd.15665

38. National Institute for Health and Care Excellence. *Adalimumab for the treatment of adults with psoriasis*; 2008.

39. Hägg D, Sundström A, Eriksson M, Schmitt-Egenolf M. Severity of Psoriasis Differs Between Men and Women: A Study of the Clinical Outcome Measure Psoriasis Area and Severity

Index (PASI) in 5438 Swedish Register Patients. *Am J Clin Dermatol* 2017;**18**:583-90. 10.1007/s40257-017-0274-0

40. Kind P, Hardman G, Macran S. *UK population norms for EQ-5D*; 1999.

41. *Institute for Clinical and Economic Review. Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value*; 2018.

42. *British National Formulary*. URL: https://bnf.nice.org.uk/ (accessed.

43. *Department of Health and Social Care. NHS reference costs*. URL: https://www.gov.uk/government/collections/nhs-reference-costs (accessed.

44. Fonia A, Jackson K, Lereun C, Grant DM, Barker JN, Smith CH. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis. *Br J Dermatol* 2010;**163**:807-16. BJD9944 [pii]

10.1111/j.1365-2133.2010.09944.x

45. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A*, et al.* Etanercept as monotherapy in patients with psoriasis. *New England Journal of Medicine* 2003;**349**:2014-22. https://dx.doi.org/10.1056/NEJMoa030409

46. Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S*, et al.* Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *Journal of the American Academy of Dermatology* 2006;**55**:598-606. https://dx.doi.org/10.1016/j.jaad.2006.05.027

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				

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	

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

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

CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Addendum II
Tildrakizumab for treating moderate to severe plaque psoriasis

Addendum II to the ERG Report

Produced by Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE)

Date 17/10/18

Background

This addendum updates the results showed in the ERG report including the correction for an error concerning how the discontinuation probability has been programmed in the company model. The company model calculated the discontinuation probability employing a shorter time-period (i.e. 12 weeks) than the cycle length used in the model (i.e. 14 weeks).

Given the error was identified at a late stage of the completing the ERG report and the implications of this error do not change the interpretation of the results, this correction was not included in the report. This addendum provides the results for all the ERG analyses including this correction.

Updated ERG tables

The uncorrected ERG analyses were reported in Tables 41-52, 54-57 of the report. The corrected results for these tables are provided below.

Table 41 (and 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]	[redacted]	[redacted]	-
ETN	UST	SEC	BSC	£236,886	[redacted]	[redacted]	[redacted]	Dominated
ADA	UST	SEC	BSC	£237,552	[redacted]	[redacted]	[redacted]	Dominated
UST	ADA	SEC	BSC	£238,284	[redacted]	[redacted]	[redacted]	Dominated
SEC	UST	ADA	BSC	£245,152	[redacted]	[redacted]	[redacted]	Ext. Dominated
GUS	UST	SEC	BSC	£262,805	[redacted]	[redacted]	[redacted]	Ext. Dominated
IXE	UST	SEC	BSC	£263,166	[redacted]	[redacted]	[redacted]	£235,292
BRO	UST	SEC	BSC	£264,355	[redacted]	[redacted]	[redacted]	£1,660,635

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

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	£225,835	[redacted]	[redacted]	[redacted]	NA	Dominates
TIL	BSC	BSC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£3,414	Dominates
ADA	BSC	BSC	BSC	£226,913	[redacted]	[redacted]	[redacted]	Dominated	Dominates
UST	BSC	BSC	BSC	£228,865	[redacted]	[redacted]	[redacted]	Ext. Dominated	Dominates
BSC	BSC	BSC	BSC	£231,461	[redacted]	[redacted]	[redacted]	Dominated	NA
SEC	BSC	BSC	BSC	£251,552	[redacted]	[redacted]	[redacted]	Ext. Dominated	£61,616
GUS	BSC	BSC	BSC	£252,490	[redacted]	[redacted]	[redacted]	Dominated	£65,125
IXE	BSC	BSC	BSC	£252,938	[redacted]	[redacted]	[redacted]	£204,724	£60,979
BRO	BSC	BSC	BSC	£254,128	[redacted]	[redacted]	[redacted]	£1,660,635	£64,225

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]	NA
Ada	Til	Sec	BSC	[redacted]	[redacted]	[redacted]	[redacted]	Ext. Dominated
Til	Ust	Sec	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£194,283
Ada	Ust	Sec	BSC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

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	£225,835	[redacted]	[redacted]	[redacted]	Dominates	£7,598	3	£8,584	4
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	£9,643	1	£11,861	1
Adalimumab	£226,913	[redacted]	[redacted]	[redacted]	Dominates	£8,903	2	£11,081	2
Ustekinumab	£228,865	[redacted]	[redacted]	[redacted]	Dominates	£7,276	4	£9,615	3
BSC	£231,461	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Infliximab	£242,313	[redacted]	[redacted]	[redacted]	£33,606	-£4,393	5	-£1,164	5
Secukinumab	£251,644	[redacted]	[redacted]	[redacted]	£61,127	-£13,579	6	-£10,278	6
Guselkumab	£252,612	[redacted]	[redacted]	[redacted]	£64,819	-£14,625	8	-£11,362	8
Ixekizumab	£253,032	[redacted]	[redacted]	[redacted]	£60,455	-£14,434	7	-£10,866	7
Brodalumab	£254,274	[redacted]	[redacted]	[redacted]	£63,937	-£15,677	9	-£12,109	9

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**
Etanercept	£226,191	[redacted]	[redacted]	[redacted]	Dominates	£7,249	4	£8,238	4
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	£10,062	2	£12,490	2
Adalimumab	£226,611	[redacted]	[redacted]	[redacted]	Dominates	£10,084	1	£12,700	1
Ustekinumab	£228,774	[redacted]	[redacted]	[redacted]	Dominates	£7,940	3	£10,566	3
BSC	£231,461	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Infliximab	£241,973	[redacted]	[redacted]	[redacted]	£33,340	-£4,206	5	-£1,053	5
Secukinumab	£251,183	[redacted]	[redacted]	[redacted]	£59,477	-£13,090	6	-£9,774	6
Ixekizumab	£252,472	[redacted]	[redacted]	[redacted]	£59,350	-£13,930	7	-£10,390	7
Guselkumab	£253,099	[redacted]	[redacted]	[redacted]	£58,986	-£14,301	8	-£10,633	8
Brodalumab	£254,420	[redacted]	[redacted]	[redacted]	£59,514	-£15,243	9	-£11,386	9

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	£225,835	[redacted]	[redacted]	[redacted]	Dominates	£7,598	4	£8,584	5
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	£9,643	2	£11,861	2
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	£10,591	1	£13,482	1
Adalimumab	£226,913	[redacted]	[redacted]	[redacted]	Dominates	£8,903	3	£11,081	3
Ustekinumab	£228,865	[redacted]	[redacted]	[redacted]	Dominates	£7,276	5	£9,615	4
BSC	£231,461	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Infliximab	£242,313	[redacted]	[redacted]	[redacted]	£33,606	-£4,393	6	-£1,164	6
Secukinumab	£251,644	[redacted]	[redacted]	[redacted]	£61,127	-£13,579	7	-£10,278	7
Guselkumab	£252,612	[redacted]	[redacted]	[redacted]	£64,819	-£14,625	9	-£11,362	9
Ixekizumab	£253,032	[redacted]	[redacted]	[redacted]	£60,455	-£14,434	8	-£10,866	8
Brodalumab	£254,274	[redacted]	[redacted]	[redacted]	£63,937	-£15,677	10	-£12,109	10

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	£225,354	[redacted]	[redacted]	[redacted]	Dominates	£8,079	4	£9,065	5
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	£9,643	2	£11,861	2
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	Dominates	£10,591	1	£13,482	1
Adalimumab	£227,439	[redacted]	[redacted]	[redacted]	Dominates	£8,377	3	£10,554	3
Ustekinumab	£228,774	[redacted]	[redacted]	[redacted]	Dominates	£7,367	5	£9,707	4
BSC	£231,461	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Infliximab	£242,005	[redacted]	[redacted]	[redacted]	£32,652	-£4,085	6	-£856	6
Guselkumab	£249,015	[redacted]	[redacted]	[redacted]	£53,795	-£11,027	7	-£7,764	7
Secukinumab	£249,955	[redacted]	[redacted]	[redacted]	£56,010	-£11,890	8	-£8,588	8
Ixekizumab	£251,350	[redacted]	[redacted]	[redacted]	£55,742	-£12,753	9	-£9,185	9
Brodalumab	£253,317	[redacted]	[redacted]	[redacted]	£61,256	-£14,720	10	-£11,152	10

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	£113,711	[redacted]	[redacted]	[redacted]	£72,153	-£5,141	1	-£4,155	1
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£61,038	-£9,105	2	-£6,886	2
Adalimumab	£121,161	[redacted]	[redacted]	[redacted]	£66,880	-£10,208	3	-£8,031	3
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£70,724	-£11,869	5	-£9,529	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£59,148	-£11,320	4	-£8,428	4
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£103,300	-£26,897	6	-£23,668	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£124,205	-£34,002	7	-£30,739	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£126,085	-£35,027	8	-£31,725	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£123,323	-£36,865	9	-£33,297	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£128,837	-£38,833	10	-£35,265	10

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	£113,711	[redacted]	[redacted]	[redacted]	£75,087	-£5,218	1	-£4,271	1
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£61,275	-£9,122	2	-£6,912	2
Adalimumab	£121,161	[redacted]	[redacted]	[redacted]	£67,175	-£10,227	3	-£8,059	3
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£70,895	-£11,880	5	-£9,546	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£58,978	-£11,303	4	-£8,403	4
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£102,782	-£26,865	6	-£23,620	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£123,558	-£33,968	7	-£30,688	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£125,399	-£34,991	8	-£31,671	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£122,477	-£36,816	9	-£33,223	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£127,953	-£38,783	10	-£35,191	10

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	£113,711	[redacted]	[redacted]	[redacted]	£14,256	£2,866	1	£7,856	4
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£17,902	£1,587	2	£9,151	2
Adalimumab	£121,161	[redacted]	[redacted]	[redacted]	£19,460	£404	4	£7,887	3
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£21,205	-£940	5	£6,864	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£19,054	£849	3	£9,825	1
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£34,914	-£14,248	6	-£4,695	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£42,096	-£21,273	7	-£11,645	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£42,896	-£22,221	8	-£12,516	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£43,119	-£23,592	9	-£13,387	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£45,047	-£25,559	10	-£15,355	10

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	NA	NA	NA
Etanercept	£116,097	[redacted]	[redacted]	[redacted]	£71,766	-£4,904	1	-£3,956	1
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£58,716	-£8,557	2	-£6,346	2
Adalimumab	£123,304	[redacted]	[redacted]	[redacted]	£64,600	-£9,669	3	-£7,501	3
Ustekinumab	£125,259	[redacted]	[redacted]	[redacted]	£68,377	-£11,292	5	-£8,958	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£57,607	-£10,905	4	-£8,006	4
Infliximab	£141,904	[redacted]	[redacted]	[redacted]	£100,470	-£26,115	6	-£22,869	6
Guselkumab	£149,069	[redacted]	[redacted]	[redacted]	£121,249	-£33,210	7	-£29,930	7
Secukinumab	£150,165	[redacted]	[redacted]	[redacted]	£123,095	-£34,226	8	-£30,906	8
Ixekizumab	£152,491	[redacted]	[redacted]	[redacted]	£120,225	-£36,007	9	-£32,414	9
Brodalumab	£154,458	[redacted]	[redacted]	[redacted]	£125,701	-£37,974	10	-£34,382	10

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	£113,711	[redacted]	[redacted]	[redacted]	£75,087	-£5,218	1	-£4,271	1
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£61,275	-£9,122	2	-£6,912	2
Adalimumab	£121,161	[redacted]	[redacted]	[redacted]	£67,175	-£10,227	3	-£8,059	3
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£70,895	-£11,880	5	-£9,546	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£58,978	-£11,303	4	-£8,403	4
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£102,782	-£26,865	6	-£23,620	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£123,558	-£33,968	7	-£30,688	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£125,399	-£34,991	8	-£31,671	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£122,477	-£36,816	9	-£33,223	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£127,953	-£38,783	10	-£35,191	10

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	£113,711	[redacted]	[redacted]	[redacted]	£14,256	£2,866	1	£7,856	4
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£17,902	£1,587	2	£9,151	2
Adalimumab	£121,161	[redacted]	[redacted]	[redacted]	£19,460	£404	4	£7,887	3
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£21,205	-£940	5	£6,864	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£19,054	£849	3	£9,825	1
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£34,914	-£14,248	6	-£4,695	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£42,096	-£21,273	7	-£11,645	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£42,896	-£22,221	8	-£12,516	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£43,119	-£23,592	9	-£13,387	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£45,047	-£25,559	10	-£15,355	10

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	£159,028	[redacted]	[redacted]	[redacted]	NA
1	TIL14 wk	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£43,144
2	ADA	UST	SEC	BSC	£164,798	[redacted]	[redacted]	[redacted]	Dominated
3	UST	ADA	SEC	BSC	£165,304	[redacted]	[redacted]	[redacted]	Dominated
10	TIL28 wk	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£43,560
4	SEC	UST	ADA	BSC	£171,336	[redacted]	[redacted]	[redacted]	Dominated
9	INF	UST	SEC	BSC	£182,266	[redacted]	[redacted]	[redacted]	Ext. Dominated
8	GUS	UST	SEC	BSC	£189,388	[redacted]	[redacted]	[redacted]	Ext. Dominated
6	IXE	UST	SEC	BSC	£192,505	[redacted]	[redacted]	[redacted]	£420,837
7	BRO	UST	SEC	BSC	£194,472	[redacted]	[redacted]	[redacted]	Dominated

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	£159,028	[redacted]	[redacted]	[redacted]	NA
1	Til14 wk	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£23,505
2	ADA	UST	SEC	BSC	£164,798	[redacted]	[redacted]	[redacted]	Dominated
3	UST	ADA	SEC	BSC	£165,304	[redacted]	[redacted]	[redacted]	Dominated
10	Til28 wk	UST	SEC	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£23,768
4	SEC	UST	ADA	BSC	£171,336	[redacted]	[redacted]	[redacted]	Dominated
9	INF	UST	SEC	BSC	£182,266	[redacted]	[redacted]	[redacted]	Ext. Dominated
8	GUS	UST	SEC	BSC	£189,388	[redacted]	[redacted]	[redacted]	Ext. Dominated
6	IXE	UST	SEC	BSC	£192,505	[redacted]	[redacted]	[redacted]	£262,712
7	BRO	UST	SEC	BSC	£194,472	[redacted]	[redacted]	[redacted]	Dominated

Tildrakizumab for treating moderate to severe plaque psoriasis

ERG exploratory scenarios for adalimumab biosimilars

Table 54 ERG alternative base case: Pairwise ICERs vs BSC and NMB rankings (Adalimumab list price)

	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	£113,711	[redacted]	[redacted]	[redacted]	£75,087	-£5,218	**1**	-£4,271	**1**
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£61,275	-£9,122	**2**	-£6,912	**2**
Adalimumab	£121,161	[redacted]	[redacted]	[redacted]	£67,175	-£10,227	**3**	-£8,059	**3**
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£70,895	-£11,880	5	-£9,546	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£58,978	-£11,303	4	-£8,403	4
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£102,782	-£26,865	6	-£23,620	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£123,558	-£33,968	7	-£30,688	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£125,399	-£34,991	8	-£31,671	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£122,477	-£36,816	9	-£33,223	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£127,953	-£38,783	10	-£35,191	10

Table 54a ERG alternative base case: Pairwise ICERs vs BSC and NMB rankings (Adalimumab biosimilar cost: assumed 20% discount)

	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	£113,711	[redacted]	[redacted]	[redacted]	£75,087	-£5,218	**2**	-£4,271	**2**
Adalimumab	£115,344	[redacted]	[redacted]	[redacted]	£40,345	-£4,411	**1**	-£2,243	**1**
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£61,275	-£9,122	**3**	-£6,912	**3**
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£70,895	-£11,880	5	-£9,546	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£58,978	-£11,303	4	-£8,403	4
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£102,782	-£26,865	6	-£23,620	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£123,558	-£33,968	7	-£30,688	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£125,399	-£34,991	8	-£31,671	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£122,477	-£36,816	9	-£33,223	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£127,953	-£38,783	10	-£35,191	10

Table 54b ERG alternative base case: Pairwise ICERs vs BSC and NMB rankings. (Adalimumab biosimilar cost: assumed 30% discount)

	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
Adalimumab	£112,436	[redacted]	[redacted]	[redacted]	£26,930	-£1,502	**1**	£666	**1**
Etanercept	£113,711	[redacted]	[redacted]	[redacted]	£75,087	-£5,218	**2**	-£4,271	**2**
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£61,275	-£9,122	**3**	-£6,912	**3**
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£70,895	-£11,880	5	-£9,546	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£58,978	-£11,303	4	-£8,403	4
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£102,782	-£26,865	6	-£23,620	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£123,558	-£33,968	7	-£30,688	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£125,399	-£34,991	8	-£31,671	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£122,477	-£36,816	9	-£33,223	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£127,953	-£38,783	10	-£35,191	10

Table 54c ERG alternative base case: Pairwise ICERs vs BSC and NMB rankings (Adalimumab biosimilar cost: assumed 40% discount)

	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
Adalimumab	£109,528	[redacted]	[redacted]	[redacted]	£13,515	£1,406	**1**	£3,574	**1**
Etanercept	£113,711	[redacted]	[redacted]	[redacted]	£75,087	-£5,218	**2**	-£4,271	**2**
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£61,275	-£9,122	**3**	-£6,912	**3**
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£70,895	-£11,880	5	-£9,546	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£58,978	-£11,303	4	-£8,403	4
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£102,782	-£26,865	6	-£23,620	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£123,558	-£33,968	7	-£30,688	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£125,399	-£34,991	8	-£31,671	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£122,477	-£36,816	9	-£33,223	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£127,953	-£38,783	10	-£35,191	10

Table 54d ERG alternative base case: Pairwise ICERs vs BSC and NMB rankings (Adalimumab biosimilar cost: assumed 60% discount)

	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**
Adalimumab	£103,711	[redacted]	[redacted]	[redacted]	Dominates	£7,223	**1**	£9,390	**1**
BSC	£106,598	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Etanercept	£113,711	[redacted]	[redacted]	[redacted]	£75,087	-£5,218	**2**	-£4,271	**2**
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£61,275	-£9,122	**3**	-£6,912	**3**
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£70,895	-£11,880	5	-£9,546	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£58,978	-£11,303	4	-£8,403	4
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£102,782	-£26,865	6	-£23,620	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£123,558	-£33,968	7	-£30,688	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£125,399	-£34,991	8	-£31,671	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£122,477	-£36,816	9	-£33,223	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£127,953	-£38,783	10	-£35,191	10

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

	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	£113,711	[redacted]	[redacted]	[redacted]	£14,256	£2,866	**1**	£7,856	4
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£17,902	£1,587	**2**	£9,151	**2**
Adalimumab	£121,161	[redacted]	[redacted]	[redacted]	£19,460	£404	4	£7,887	**3**
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£21,205	-£940	5	£6,864	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£19,054	£849	**3**	£9,825	**1**
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£34,914	-£14,248	6	-£4,695	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£42,096	-£21,273	7	-£11,645	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£42,896	-£22,221	8	-£12,516	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£43,119	-£23,592	9	-£13,387	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£45,047	-£25,559	10	-£15,355	10

Table 55a ERG alternative base case (including additional assumption that utility of BSC = baseline utility): Pairwise ICERs vs BSC and NMB rankings (Adalimumab biosimilar cost: assumed 20% discount)

	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	£113,711	[redacted]	[redacted]	[redacted]	£14,256	£2,866	**2**	£7,856	4
Adalimumab	£115,344	[redacted]	[redacted]	[redacted]	£11,688	£6,220	**1**	£13,704	**1**
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£17,902	£1,587	**3**	£9,151	**3**
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£21,205	-£940	5	£6,864	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£19,054	£849	4	£9,825	**2**
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£34,914	-£14,248	6	-£4,695	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£42,096	-£21,273	7	-£11,645	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£42,896	-£22,221	8	-£12,516	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£43,119	-£23,592	9	-£13,387	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£45,047	-£25,559	10	-£15,355	10

Table 55b ERG alternative base case (including additional assumption that utility of BSC = baseline utility): Pairwise ICERs vs BSC and NMB rankings (Adalimumab biosimilar cost: assumed 30% discount)

	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
Adalimumab	£112,436	[redacted]	[redacted]	[redacted]	£7,802	£9,129	**1**	£16,612	**1**
Etanercept	£113,711	[redacted]	[redacted]	[redacted]	£14,256	£2,866	**2**	£7,856	4
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£17,902	£1,587	**3**	£9,151	**3**
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£21,205	-£940	5	£6,864	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£19,054	£849	4	£9,825	**2**
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£34,914	-£14,248	6	-£4,695	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£42,096	-£21,273	7	-£11,645	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£42,896	-£22,221	8	-£12,516	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£43,119	-£23,592	9	-£13,387	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£45,047	-£25,559	10	-£15,355	10

Table 55c ERG alternative base case (including additional assumption that utility of BSC = baseline utility): Pairwise ICERs vs BSC and NMB rankings (Adalimumab biosimilar cost: assumed 40% discount)

	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
Adalimumab	£109,528	[redacted]	[redacted]	[redacted]	£3,915	£12,037	**1**	£19,521	**1**
Etanercept	£113,711	[redacted]	[redacted]	[redacted]	£14,256	£2,866	**2**	£7,856	4
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£17,902	£1,587	**3**	£9,151	**3**
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£21,205	-£940	5	£6,864	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£19,054	£849	4	£9,825	**2**
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£34,914	-£14,248	6	-£4,695	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£42,096	-£21,273	7	-£11,645	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£42,896	-£22,221	8	-£12,516	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£43,119	-£23,592	9	-£13,387	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£45,047	-£25,559	10	-£15,355	10

Table 55d ERG alternative base case (including additional assumption that utility of BSC = baseline utility): Pairwise ICERs vs BSC and NMB rankings (Adalimumab biosimilar cost: assumed 60% discount)

	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**
Adalimumab	£103,711	[redacted]	[redacted]	[redacted]	Dominates	£17,854	**1**	£25,337	**1**
BSC	£106,598	[redacted]	[redacted]	[redacted]	NA	NA	NA	NA	NA
Etanercept	£113,711	[redacted]	[redacted]	[redacted]	£14,256	£2,866	**2**	£7,856	4
Tildrakizumab 100mg (14 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£17,902	£1,587	**3**	£9,151	**3**
Ustekinumab	£123,146	[redacted]	[redacted]	[redacted]	£21,205	-£940	5	£6,864	5
Tildrakizumab 100mg (28 wk)	[redacted]	[redacted]	[redacted]	[redacted]	£19,054	£849	4	£9,825	**2**
Infliximab	£139,953	[redacted]	[redacted]	[redacted]	£34,914	-£14,248	6	-£4,695	6
Guselkumab	£147,126	[redacted]	[redacted]	[redacted]	£42,096	-£21,273	7	-£11,645	7
Secukinumab	£148,228	[redacted]	[redacted]	[redacted]	£42,896	-£22,221	8	-£12,516	8
Ixekizumab	£150,599	[redacted]	[redacted]	[redacted]	£43,119	-£23,592	9	-£13,387	9
Brodalumab	£152,566	[redacted]	[redacted]	[redacted]	£45,047	-£25,559	10	-£15,355	10

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from CRD and CHE Technology Assessment Group, University of York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 19 October 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Factual inaccuracy - company error

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th></tr>
<tr>
<td>
Factual inaccuracy in the proportion of patients who had received prior non-biologic systemic therapy.

This is because information provided by the company in response to ERG clarification question A3 was incorrect.

The report refers to this data in a number of places:

Page 15, Section 1.3

Moreover, the proportion of patients previously treated with a systemic non-biologic therapy across both reSURFACE trials (7-8%)…

Page 42, Section 4.2.4.1

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

Page 46, Section 4.2.5

The ERG note these are lower (<10% in all arms in reSURFACE1 and reSURFACE2)..

Page 47, Section 4.2.6
</td>
<td>
The proportion of patients who received prior systemic non-biologic therapy is incorrect. Revised numbers are provided below

reSURFACE 1 (FAS Part 1 and Observed Cases)
<table>
<tr><th></th><th>Tildrakizumab 100mg N=309</th><th>Tildrakizumab 200mg N=308</th><th>Placebo N=154</th><th>Total N=771</th></tr>
<tr><td colspan="5">Previous treatment with a systemic non-biologic therapy, n (%)</td></tr>
<tr><td>No</td><td>244 (78.96%)</td><td>230 (74.68%)</td><td>113 (73.38%)</td><td>587 (76.13%)</td></tr>
<tr><td>Yes</td><td>65 (21.04%)</td><td>78 (25.32%)</td><td>41 (26.62%)</td><td>184 (23.87%)</td></tr>
</table>

reSURFACE 2 (FAS Part 1 and Observed Cases)
<table>
<tr><th></th><th>Tildrakizumab 100mg N=307</th><th>Tildrakizumab 200mg N=314</th><th>Placebo N=156</th><th>Etanercept 50mg N=313</th><th>Total N=1090</th></tr>
<tr><td colspan="6">Previous treatment with a systemic non-biologic therapy, n (%)</td></tr>
<tr><td>No</td><td>184 (59.93%)</td><td>182 (57.96%)</td><td>95 (60.90%)</td><td>193 (61.66%)</td><td>654 (60.00%)</td></tr>
<tr><td>Yes</td><td>123 (40.07%)</td><td>132 (42.04%)</td><td>61 (39.10%)</td><td>120 (38.34%)</td><td>436 (40.00%)</td></tr>
</table>
</td>
<td>
Almirall would like to apologise as the factual inaccuracy in the ERG report is due to incorrect information which was provided by Almirall to the ERG in the response to ERG clarification question A3. This was due to a programming error which was unfortunately not picked up prior to submitting the information to the ERG.

Corrected information is provided as a separate appendix to this response in case the ERG would like the opportunity to review it, although we appreciate that the ERG is under no obligation to consider additional information at this stage.
</td>
</tr>
</table>

This contrasts with the small (around 8%) number of patients who received previous non-biologic systemic agent.. Page 75, Section 4.6 *In addition the proportion of patients previously treated with a systematic non-biologic therapy at baseline across both trials (7-8%)..*	Non-biologic systemic therapy included in these data: fumaric acid, methotrexate, methotrexate sodium, ciclosporin, acitretin, calcium monoethyl fumarate (+) dimethyl fumarate (+) magnesium monoethyl fumarate (+) zinc monoethyl fumarate, dimethyl fumarate and apremilast	

Issue 2 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment
Page 13, Section 1.2 Page 60, Section 4.3 Page 75, NMA The list (shown below) of comparator treatments included in the NMA is incorrect and should include guselkumab but not risankizumab *'adalimumab, apremilast, brodalumab etanercept, ixekizumab, risankizumab secukinumab, ustekinumab and DMF'.*	In line with Section B.2.9 of the CS the list should read *adalimumab, apremilast, brodalumab etanercept, <u>guselkumab</u>, ixekizumab, ~~risankizumab~~, secukinumab, ustekinumab and DMF.*	The NMA presented information for adalimumab, apremilast, brodalumab etanercept, guselkumab, ixekizumab, secukinumab, ustekinumab and DMF. Risankizumab was included in the systematic literature review which was conducted on a global basis and 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. (CS response to ERG clarification Question A10)

Issue 3 Incomplete representation of efficacy results

Description of problem	Description of proposed amendment	Justification for amendment
Page 13, Section 1.2 Amend to clarify that tildrakizumab 200mg (but not 100mg) was statistically better than etanercept for clear or minimal PGA at 12 weeks. *'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.'*	Revise text as below to align with CS Section 4.2.4.2 *'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 <u>for 100mg</u>'.*	Correct presentation of efficacy results.

Issue 4 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment
Page 14, Section 1.2 The 8% figure in the text below is incorrect *'The most frequent adverse event up to week 12 across the trials groups receiving tildrakizumab was nasopharyngitis which ranged in incidence from around 8% to 13%'*	To amend the text as follows in line with the figures in Tables 23 and 24 of the CS *'The most frequent adverse event up to week 12 across the trials groups receiving tildrakizumab was nasopharyngitis which ranged in incidence from around ~~8~~6% to 13%'.*	Factual inaccuracy.

Issue 5 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment
Page 28, Section 3.3 The text states that the SmPC refers to patients with PASI>20 which is incorrect. *and indeed the anticipated licence of tildrakizumab makes specific reference to patients whose PASI is > 20.*	The CS Section B.2.7 includes subgroup data for the group of patients with PASI ≥20. *and ~~indeed~~ the ~~anticipated licence of~~ CS for tildrakizumab ~~makes specific reference to~~includes subgroup data for patients whose PASI is ≥ 20.*	The SmPC refers to patients with 'a high disease burden' but does not refer to a specific PASI level in relation to this. The CS Section B.2.7 states that to better identify patients with high disease burden, subpopulation analyses were undertaken for patients in the reSURFACE studies. A post hoc analysis of baseline severity data included patients with PASI ≥20.

Issue 6 Misleading description of patient numbers

Description of problem	Description of proposed amendment	Justification for amendment
Page 35-36, Section 4.2.1.2 Point for clarification *For both trials the FAS for the analysis of data up to 12 weeks (Part 1 - the placebo controlled phase of the trials) was 'all patients who have received at least one dose of the study medication' (tildrakizumab 100mg n=309, tildrakizumab 200mg n=308, placebo n=154). 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 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)' (tildrakizumab 100mg n=307, tildrakizumab 200mg n=314, placebo n=156, etanercept n=313).*	To clarify patient numbers in the FAS for part 1 of the reSURFACE studies as per CS Section B.2.6.3. Tables 12 and 13, the text should be corrected to *For both trials the FAS for the analysis of data up to 12 weeks <u>in Part 1 (the</u> placebo controlled phase of the trials) was 'all patients who have received at least one dose of the study medication' (reSURFACE 1 - tildrakizumab 100mg n=309, tildrakizumab 200mg n=308, placebo n=154; <u>reSURFACE 2 - tildrakizumab 100mg n=307, tildrakizumab 200mg n=314, placebo n=156, etanercept n=313</u>). 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 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) ~~(tildrakizumab 100mg n=307, tildrakizumab 200mg n=314, placebo n=156, etanercept n=313).~~*'.	To clarify that both sets of patient numbers provided in the text relate to Part 1 of the reSURFACE studies and to accurately reflect the CS.

Issue 7 Factual inaccuracy

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th></tr>
<tr><td>Page 40, Table 3
Some data values are incorrectly reported in the table (DLQI week 28</td><td>Corrected values are shown below in line with Tables 17 and 18 in the CS
<table>
<tr><td rowspan="4">DLQI score of 0 or 1 Responders, n (%)
(no imputation for missing data, treated as missing)</td><td>12</td><td>126 (41.~~5~~4)</td><td>132 (44.~~2~~1)</td></tr>
<tr><td>28</td><td>[redacted]152 (52.4)</td><td>[redacted]164 (56.7)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td></tr>
</table></td><td>Incorrect data reported in table</td></tr>
</table>

Issue 8 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment
Correction of data values Page 41, Section 4.2.4.1 *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 (93.6%), etanercept 289/313 (92.3%))* Page 42, Section 4.2.4.1 *The most commonly used previous biologic in the tildrakizumab 100mg, tildrakizumab 200mg, placebo and etanercept arm was adalimumab[redacted] respectively*	Corrected text based on patient numbers in Appendix D Figure 4 should read as follows *To summarise, 1090 patients were randomised, 1026 (~~96~~94.1%) 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 (~~93.6~~91.0%), etanercept 289/313 (92.3%))* Corrected text based on Table 8 in ERG clarification response *The most commonly used previous biologic in the tildrakizumab 100mg, tildrakizumab 200mg, placebo and etanercept arm was adalimumab[redacted] respectively*	Correction of values

Issue 9 Point of clarification reporting patient data

Description of problem	Description of proposed amendment	Justification for amendment
Page 40, Table 3 and Page 44, Table 4 The tables report patient numbers and percentages for each endpoint but do not appropriately describe differing patient numbers in the groups considered. Data for DLQI score is incorrectly identified as mean change from baseline.	For clarity the tables should include the patient numbers per group used in each analysis. DLQI data comparing tildrakizumab to placebo are differences in least square means.	The patient numbers and percentages are reported for each endpoint but do not take account of the fact that the number of patients in each treatment group (relative to the number of responders) is different at Week 12 and 28 and different for the DLQI data and EQ-5D data (i.e. observed data not NRI data).

Issue 10 Confidentiality mark up required

Description of problem	Description of proposed amendment	Justification for amendment
Page 39, Section 4.2.3.1 Confidentiality mark up and correction of one value *The most commonly used in the tildrakizumab 100mg, tildrakizumab 200mg and placebo arm was etanercept; 57.7%, 52.2% and 55.9% respectively, followed by adalimumab; 28.2%, 43.7% and 32.4%, 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; 7.44%, 7.79% and 7.14%, respectively*.	As per the company ERG Clarification response (Tables 6 and 9) details of prior therapies should be marked as confidential [AIC] as follows: *The most commonly used in the tildrakizumab 100mg, tildrakizumab 200mg and placebo arm was etanercept; [redacted] and [redacted]% respectively, followed by adalimumab; [redacted], [redacted]% and [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]%, [redacted]% and [redacted]%, respectively*.	Data are academic in confidence prior to potential publication

Description of problem	Description of proposed amendment	Justification for amendment
Page 15, Section 1.3 *Moreover, the proportion of patients previously treated with a systemic non-biologic therapy across both reSURFACE trials (7-8%)…* Page 46 *The ERG note these are lower (<10% in all arms in reSURFACE1 and reSURFACE2)..* Page 47 *This contrasts with the small (around 8%) number of patients who received previous non-biologic systemic agent..* Page 75, Section 4.6 *In addition the proportion of patients previously treated with a systematic non-biologic therapy at baseline across both trials (7-8%)..*	Values should be marked as confidential [AIC] in line with the Company ERG Clarification response (Tables 9 and 10) as follows Page 15, Section 1.3 *Moreover, the proportion of patients previously treated with a systemic non-biologic therapy across both reSURFACE trials ([redacted]%)…* Page 46 *The ERG note these are lower ([redacted] in all arms in reSURFACE1 and reSURFACE2)..* Page 47 *This contrasts with the small (around [redacted]) number of patients who received previous non-biologic systemic agent..* Page 75, Section 4.6 *In addition the proportion of patients previously treated with a systematic non-biologic therapy at baseline across both trials ([redacted]%)..*	Data are academic in confidence. We appreciate that in Issue 1 we have identified that these numbers are incorrect so may be replaced, but the replacement values should also be marked as AIC.
Page 109, Footer to Table 32 Page 110, Footer to Table 33 Page 114, Section 5.2.12. Text [redacted] should be confidential	Footers to Tables 32 and 33 *†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] Page 114 [redacted]	Data are commercial in confidence as the price is not in the public domain. Apologies as this was an error on the part of the company and should have been marked as CIC in Table 35 of the

Description of problem	Description of proposed amendment	Justification for amendment
		company submission.
Page 71, Table 15 Page 73, Table 16 All values in Table 15 and Table 16 should be marked as AIC	All data values in the tables are AIC based on Tables 99 and 100 in the Company ERG clarification response	This information is AIC. Apologies this was underlined but not fully identified as AIC in the tables provided with the clarification response.

Issue 11 Factual inaccuracy

Description of problem	Description of proposed amendment
Page 46, Table 5 and text immediately underneath the table Factual inaccuracy. Some of the data supplied in Table 16 of the company response to the ERG clarification	We suggest that Table 5 could be replaced with the following table

	N (%) achieving PASI 75 at week 28		
	TIL 100 mg (n=593)		TIL 20
	YES	NO	YES
PASI<50 wk12	[redacted]	[redacted]	[redacted]
PASI 50-75 wk12	[redacted]	[redacted]	[redacted]

and the text revised as follows:

[redacted]

questions has been misinterpreted and as a consequence some calculations in Table 5 along with the conclusion shown underneath the table are incorrect.	

Issue 12 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment
Page 47, Table 6, 12 week data Factual inaccuracy Calculations are incorrect and do not correlate with Table 17 of the company ERG clarification response.	Revised text is shown below [redacted]	Correction of patient numbers in subgroup analyses

Issue 13 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment
Page 48 Section 4.2.7 Figure 5 heading Factual inaccuracy as heading refers to incorrect part of CS *(CA Appendix E Table 17)*	The reference in the heading should be amended to ~~*(CA Appendix E Table 17)*~~(CS Appendix E Figure 16)	To correct the cross referencing to correct part of CS.

Issue 14 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment
Page 52, Section 4.2.9.1 Factual inaccuracy *Of those commencing phase two, 292/308 (94.8%) of patients completed.*	The sentence should be corrected as follows in line with CS Appendix D Figure 3 *Of those commencing phase two, ~~292/308 (94.8%)~~292/339 (86.1%) of patients completed*	Correction of patient numbers and proportion entering phase two of the study.

Issue 15 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment
Page 52, Section 4.2.9.1 Factual inaccuracy and typographical error '*In addition, in the licence dose arms, 17% and 19%, respectively, had received prior to biologic therapy….'*	The corrected text should read as follows in line with Table 3 included in the Company response to the ERG clarification question *'In addition, in the licence dose arms, 17% and ~~19~~22%, respectively, had received prior ~~to~~ biologic therapy……'*	Factual inaccuracy

Issue 16 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment
Page 54, Section 4.2.9.4 Factual inaccuracy *Frequency of hypertension was found to be dose related, with 8/308 patients experiencing the AE who received tildrakizumab and 0/48 experiencing the AE who received placebo.*	The text should be corrected as below as per data provided in CS Appendix F page 229: '*Frequency of hypertension was found to be dose related, with ~~8/308~~9/308 patients experiencing the AE who received tildrakizumab and ~~0/48~~0/45 experiencing the AE who received placebo'*	Correction of a factual inaccuracy

Issue 17 Removal of confidentiality mark up

Description of problem	Description of proposed amendment	Justification for amendment
Page 56, 'Part 3' of the trials Unmarking of AIC data now that data are in the public domain The CS states that, of the PASI 75 responders at week 28 in reSURFACE 1 [redacted] on tildrakizumab 100mg and [redacted] 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] and [redacted] of patients at Week 64.	Some data can be unmarked. The corrected text should read as follows: 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 [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 [redacted] (74.6%) of patients at Week 64.	Unmarked data are no longer AIC

Issue 18 Factual inaccuracy – company error

Description of problem	Description of proposed amendment	Justification for amendment
Page 57, Table 12 and text immediately above the table. Factual inaccuracy – incorrect information provided in Table 4 of the company response to the ERG clarification questions *'the figures are unusually different for the 100mg and 200mg groups being [redacted] and [redacted] respectively, based on the data provided by the company in* ***Error! Reference source not found.****.'*	The data for the number of patients on tildrakizumab 100mg in reSURFACE 2 who did / did not enter the long term extension study are incorrect in Table 4 of the company response to the ERG clarification questions. The cells in the last two rows of the penultimate column of Table 12 in the ERG report should read: [redacted] and the corresponding text amended as follows *the 100mg and 200mg groups being [redacted] respectively.*	Apologies as two values in the data provided by the company in Table 4 of the company's ERG clarification response were incorrect and hence the ERG calculation is incorrect.

Issue 19 Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment
Page 59, Adverse events in Part 1 of the trials. Factual inaccuracy *'In reSURFACE 1 the incidence of nasopharyngitis ranged between 5% (in the placebo group) and 8% (in the tildrakizumab 200mg group)'.*	The corrected text should read as follows in line with CS Section B.2.10 Table 23 *'In reSURFACE 1 the incidence of nasopharyngitis ranged between 5% (in the placebo group) and 8% (in the tildrakizumab ~~200~~100mg group)'.*	To correctly attribute the incidence of nasopharyngitis to the 100mg tildrakizumab group.

Issue 20 Incorrect representation of study exclusions from NMA

Description of problem	Description of proposed amendment	Justification for amendment
Page 61, Section 4.3 Factual inaccuracy. The following statement is incorrect in stating the IMMhance study was missed in the SLR. *'Other trials appear to have been missed because they were too recent: the CLARITY trial of secukinumab versus ustekinumab was available only in grey literature and the IMMhance trial only from a conference abstract'.*	This statement should be removed *Other trials appear to have been missed because they were too recent: the CLARITY trial of secukinumab versus ustekinumab was available only in grey literature ~~and the IMMhance trial only from a conference abstract~~.*	Factual inaccuracy The ERG suggest that the IMMhance trial was missed because it was recently published and only reported in a conference abstract. This is incorrect. The IMMhance abstracts were identified and excluded (see CS Appendix D Table 10). IMMhance compared risankizumab with placebo which is not a comparison of interest in the current NMA.

Description of problem	Description of proposed amendment	Justification for amendment
Page 61, Section 4.3 Factual inaccuracy as the study was not omitted in error. *The omission of one placebo comparison of apremilast appears to be an error.*	This statement should be removed ~~*The omission of one placebo comparison of apremilast appears to be an error.*~~	Factual inaccuracy The ERG flags some specific studies that were included in other NMAs but excluded from the CS and the ERG agree that they are reasonable given the eligibility criteria used. However, they state that one trial was omitted in error. This trial compared placebo, apremilast 20mg BID and apremilast 20mg QD. The dose of interest to the NMA was apremilast 30mg hence this exclusion was not an error.
Page 61, Section 4.3 Factual inaccuracy. The following statement on the reason the IXORA study was excluded is incorrect '*….and the IXORA-S trial of ixekizumab versus ustekinumab was deemed to involve ineligible interventions (Ixekizumab 160mg loading versus ustekinumab by 'weight).*	Suggest adding the maintenance dose as well as the loading dose *'…and the IXORA-S trial of ixekizumab versus ustekinumab was deemed to involve ineligible interventions (Ixekizumab 160mg loading dose <u>then 80mg every 2 weeks for 12 weeks</u> versus ustekinumab by weight)'*	Factual inaccuracy The ERG state that IXORA-S was excluded because it was deemed to have ineligible interventions and then in brackets state that the doses were ixekizumab 160mg loading dose versus ustekinumab by weight. This is correct but the reason this study was excluded was because, after the loading dose, patients received 80mg every 2 weeks. The eligible dose of ixekizumab in the CS was 80mg every 4 weeks . (CS Appendix D Table 10).

Issue 21 Misleading statement on the impact of infliximab exclusion from the NMA

Description of problem	Description of proposed amendment	Justification for amendment
Page 127, Table 40 The report states that the potential impact of the exclusion of the infliximab trials from the NMA is unclear (row in table relating to section 5.2.6 of the ERG critique: treatment effectiveness and extrapolation). *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.*	In line with the company response to ERG Clarification question A13, the current text in column three should be replaced with the following: ~~*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.*~~ *'Negligible impact expected'*	The relative risk values generated from the networks with and without infliximab were almost identical (with the exception of infliximab). Given the similarity we believe it is clear that using the updated NMA will not affect the ICERs so the current statement that the effect is 'unclear' is misleading.

Issue 22 Misleading statement on the importance of non-responder costs

Description of problem	Description of proposed amendment	Justification for amendment
Page 128, Table 40. It is stated that the inclusion of non-responder costs has a potentially important impact of the ICERs (row in table relating to section 5.2.10 of the ERG critique: non responder costs). *'Potentially important as differences in the costs between some sequences are small.'*	The current text in column three should be replaced with the following: ~~*Potentially important as differences in the costs between some sequences are small.*~~ *Negligible impact expected'*	We believe the current statement has the potential to over-state the importance of non-responder costs on the overall results of the analysis. This can be illustrated by the scenario analysis that was run by the ERG on this point (Section 6.9) as the inclusion of non-responder costs led to no changes in the results. This led to the following conclusion from the ERG 'this suggests that the cost of non-response does not appear to be an important driver of cost-effectiveness'. Therefore, the text in the table contradicts the ERGs earlier statement.

Issue 23 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment
Page 32, Section 4.2 Typographical error '*In the CS, only the two phase II trials …….*'	As per Section B.2.2 of the CS, the text should read '*In the CS, only the two phase III trials …….*'	Typographical error to correct the phase of the pivotal trials
Page 19, Section 1.5 point (iii) *The company provided further rationale for a 28 week induction period and a scenario analysis evaluating the 28 induction period.*	The sentence should read *The company provided further rationale for a 28 week induction period and a scenario analysis evaluating the 28 week induction period.*	Typographical error
Page 20, Section 1.5 point (v) Typographical error *……the committee concluded that BSC cost estimates were likely to be closer to Fonia et al. than to the estimates from NICE CG53.Based*	The text should read *…the committee concluded that BSC cost estimates were likely to be closer to Fonia et al. than to the estimates from NICE CG153. Based*	Typographical error to correct the NICE clinical guideline number
Page 34 Trial design Missing text *Schematic diagrams detailing information on the trial design for reSURFACE1 and reSURFACE2 are presented in and.'*	The text should read *Schematic diagrams detailing information on the trial design for reSURFACE1 and reSURFACE2 are presented in Figure 1 and Figure 2.'*	Typographical error – to complete the sentence

Description of problem	Description of proposed amendment	Justification for amendment
Page 46, Section 4.2.5 Typographical error *In the company's response to clarification the number and proportion of patients previously treated with a systematic non-biologic therapy at baseline were provided for both trials. The ERG note these are lower (<10% in all arms in reSURFACE1 and reSURFACE2) than would be seen in clinical practice, where all patients are expected to receive systematic non-biologic therapy prior to commencing biologic treatment options.*	Replace the word systematic with systemic and mark <10% as AIC so the text reads 'In the company's response to clarification the number and proportion of patients previously treated with a ~~systematic~~ systemic non-biologic therapy at baseline were provided for both trials. The ERG note these are lower ([redacted] in all arms in reSURFACE1 and reSURFACE2) than would be seen in clinical practice, where all patients are expected to receive ~~systematic~~ systemic non-biologic therapy prior to commencing biologic treatment options.'	Typographical error and confidentiality mark up.
Typographical errors Page 12 , Section 1.1 Page 14, Section 1.2 and Section 1.3 Page 24, Section 1.7 Page 58, Section 4.2.10 Page 65, Section 4.3.2 Page 70, Stage III NMA Page 85, Table 18 Page 95, ERG commentary Page 135, Section 6.4 Page 160, Section 8	Correction of drug names *~~dimethey~~l fumarate should read dimethyl fumarate* ~~Tilrakizumab~~ should read tildrakizumab ~~gusulkumab~~ should read guselkumab ~~brosalumab~~ should read brodalumab ~~Secukinimab~~ should read secukinumab ~~tildrakizumb~~ should read tildrakizumab ~~risakinzumab~~ should read risankizumab ~~ustekinumab~~ should read ustekinumab ~~gusulkumab~~ should read guselkumab ~~tilrakizumab~~ should read tildrakizumab	Correction to drug names.

Description of problem	Description of proposed amendment	Justification for amendment
Typographical errors whereby the Stage III NMA is incorrectly identified as Stage II NMA Page 65 Page 70 Page 73 – heading of Table 16	Revised text is shown below *To check the reliability of the Stage ~~II~~III NMA the ERG….* *To check the reliability of the Stage ~~II~~III NMA the ERG ….* *Table 16 Comparison of direct and indirect evidence for the Stage ~~II~~III analysis:*	To correctly identify the NMA analysis.
Page 75, Section 4.6 The PASI value should be PASI ≥20 *For patients with a baseline PASI >20 the evidence for a better response with the 200mg dose (at week 28) is a little stronger.*	Revised text should read *For patients with a baseline PASI ≥20 the evidence for a better response with the 200mg dose (at week 28) is a little stronger*	Typographical error.
Page 89, ERG Commentary Typographical error *Some patients with initial partial response may subsequently improve with continued treatment beyond 28 weeks.to be appropriate*”.	Deletion of additional text. *Some patients with initial partial response may subsequently improve with continued treatment beyond 28 weeks.~~to be appropriate~~*”.	To accurately reflect SmPC wording.
Page 66, Section 4.4.1 Typographical error, missing word ‘week’ *‘whether the 12 or 16 data are used should reflect the appropriate time for assessment for a given treatment (as reflected in the main trials’ primary endpoint).’*	Revised text should read *‘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).’*	Typographical error.