NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Brodalumab for treating moderate to severe plaque psoriasis [ID878]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Brodalumab for treating moderate to severe plaque psoriasis [ID878]

Contents:

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

Pre-meeting briefing

Brodalumab for treating moderate to severe plaque psoriasis in adults [ID878]

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

Key issues for consideration
Clinical effectiveness

- What is the likely position of brodalumab in the treatment pathway for psoriasis in NHS clinical practice?
- Are the results from AMAGINE trials generalisable to the eligible population for brodalumab in the NHS with respect to:
  - Disease severity?
  - Previous biological therapy?
  - Age?
- Which network meta-analysis is preferred for decision making: placebo-adjusted or unadjusted?
- What is the minimal clinically important difference for the Psoriasis Area and Severity Index? PASI 75 or PASI 90?
- Is brodalumab a clinically effective treatment?
  - Does treatment effect wane (evidence? no data on relapse rates)

Key issues for consideration
Cost effectiveness

- How should the cost effectiveness of brodalumab be assessed?
  - in a treatment sequence of systemic agents with brodalumab compared with a sequence without brodalumab?
  - brodalumab single treatment compared with another single systemic agent?
- Which analysis is preferred? Company's fully incremental analysis of 9 treatment sequences or ERG's net monetary benefit framework of individual treatments vs best supportive care?
- How should discontinuation from treatment be modelled?
- How should utility values be modelled? Company's adjusted for baseline DLQI or ERG's adjusted for baseline EQ-5D?
- Which dosing regimen of brodalumab should be used during induction? Company's 7 dose or ERG's 8 dose?
- Should non-responder costs be included in the model?
- Equality issues
- Innovation

Plaque psoriasis

- Chronic inflammatory condition characterised by flaky, scaly, itchy and red plaques on the skin
- May affect the scalp, elbows, knees, lower back and sometimes the face, groin, armpits and behind the knees
- Unpredictable, relapsing and remitting course
- Graded as mild, moderate or severe (based on location, area affected, severity of lesions and impact on individual)
- Prevalence of psoriasis in England:
  - 1.75% (959,000)
    - 15% classified as moderate (144,000)
    - 5% classified as severe (50,000)
- Plaque psoriasis is the most common type (90%; 863,000)
- Associated with comorbidities such as depression, anxiety, arthritis, cardiovascular disease

Brodalumab
(Kyntheum)
Leo Pharma

Marketing authorisation
"moderate to severe plaque psoriasis in adults who are candidates for systemic therapy"

Mechanism of action

- recombinant fully human monoclonal immunoglobulin IgG2 antibody
- binds to proteins with interleukin-17 receptor-A
- inhibits inflammation of the skin

Administration and dose

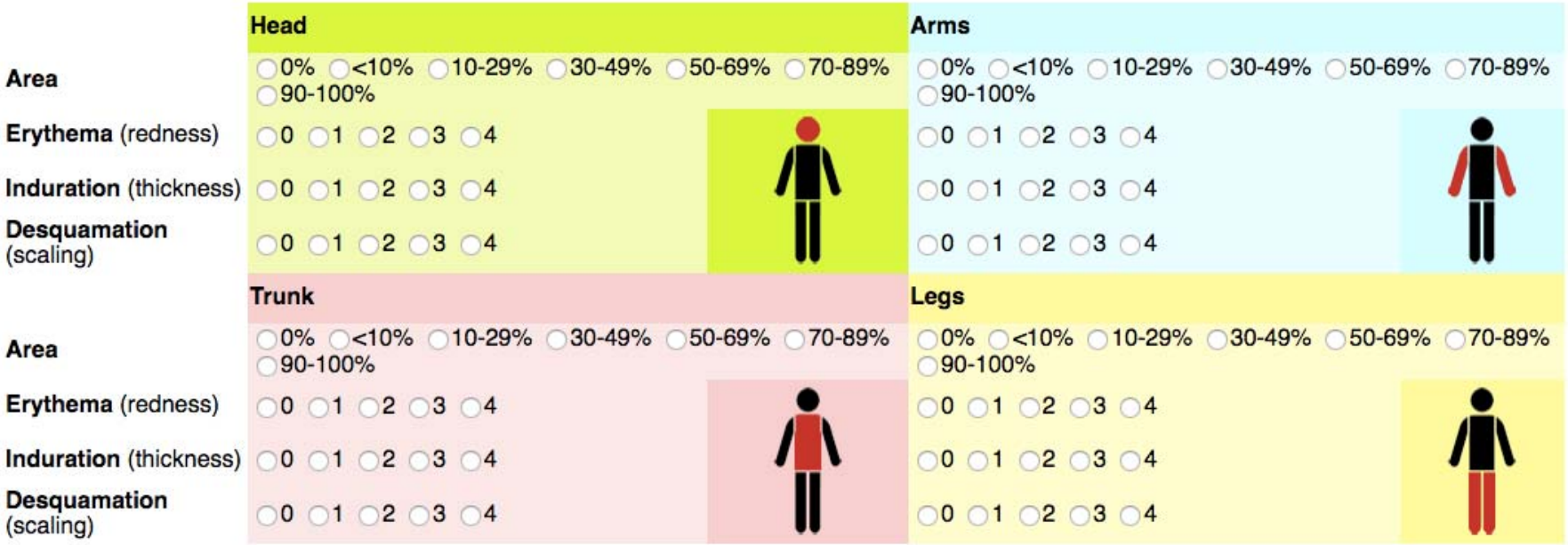
Subcutaneous injection

- **Weeks 1-3:** 210 mg every week
- **Weeks 4 onwards:** 210 mg every 2 weeks

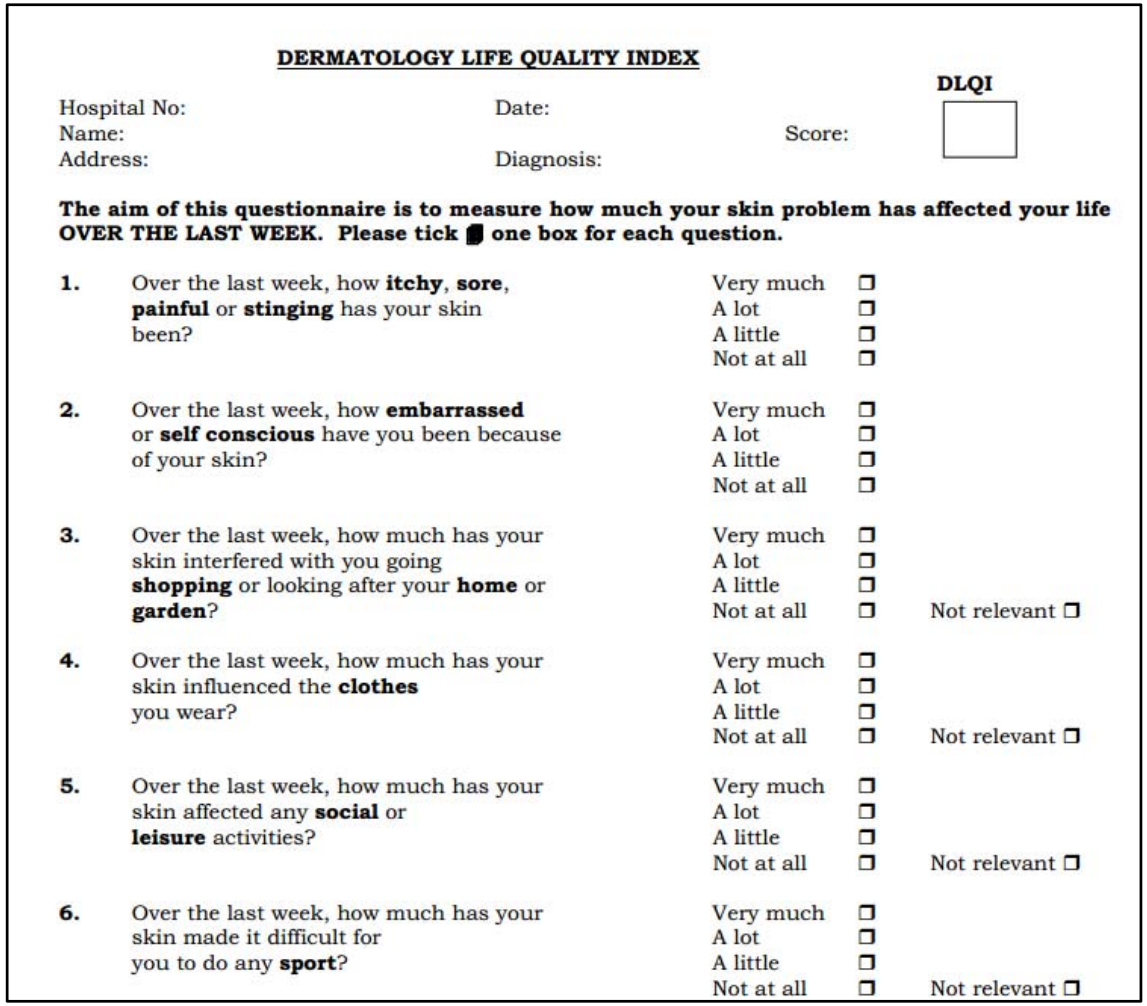
If no response, discontinue treatment after 12 to 16 weeks
If partial response, continued use may lead to improvement after 16 weeks

Measuring Clinical Effectiveness Psoriasis Area and Severity Index (PASI)

- Weighted score based on 4 affected areas
  - range from 0 to 72
  - no disease is 0; moderate is 10; severe is >10
- Response considered as PASI 50, PASI 75, PASI 90, PASI 100
  - PASI 75: ≥75% reduction in PASI score from baseline (clinically important difference according to British Association of Dermatologists guidelines)
  - PASI 100: 100% reduction in PASI score (i.e. to 0)



Measuring health-related quality of life
Dermatology Life Quality Index (DLQI)



DERMATOLOGY LIFE QUALITY INDEX

Hospital No: Date:
Name: Score: DLQI
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ■ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much ❒ A lot ❒ A little ❒ Not at all ❒	Not relevant ❒

- **10 questions:** symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment
- each item scores 0-3 (3 = worst impact)
- range from 0 to 30
- 5 point improvement (clinically important)
- proportion of patients with scores of 0 or 1 (indicate psoriasis has no effect on life at a specific visit)

Treatment pathway

1st

Topical therapy
corticosteroid, vitamin D, vitamin D analogues, coal tar

2nd

Phototherapy
ultraviolet B (narrow and broad band), psoralen + ultraviolet A [PUVA]

3rd

Systemic non-biological therapy
methotrexate, ciclosporin, acitretin

4th

Systemic biological therapy

Severe (PASI ≥10 & DLQI >10)

adalimumab (TA146)
etanercept (TA103)
ixekizumab (TA442)
secukinumab (TA350)
ustekinumab (TA180)

Very severe (PASI ≥20 & DLQI >18)

infliximab (TA134)

Severe (PASI ≥10 & DLQI >10)

apremilast (TA419)
dimethyl fumarate (TA475)

Brodalumab for moderate to severe psoriasis?

LEGEND

TNF-α inhibitor
IL-17 inhibitor
IL-12/IL-23 inhibitor
PDE-4 inhibitor
Th1 and Th17 → Th2

BSC

Best supportive care

Patient feedback

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

- Psoriasis is a lifelong condition that can be distressing at any level of severity and for some debilitating, affecting all aspects of life, physically, psychologically, socially and financially
- Individuals respond differently to treatments and a range of options is needed
- People want to see:
  - immediate improvement of symptoms (reduction in itching, scaling, redness, clearance and pain)
  - limited inconvenience on lifestyle and daily activities
  - no adverse reactions
- Topical medicines are ‘messy’ and time consuming
- Phototherapy is beneficial but needs regular appointments and is difficult if used
- Outcome assessment should consider high impact sites such as face, hands, feet and genitals
- Potential disadvantage of brodalumab is prescribing warning for people with a history of depression and suicide ideation
- Unmet need for people with moderate psoriasis for whom topical treatments and biological therapies are not suitable

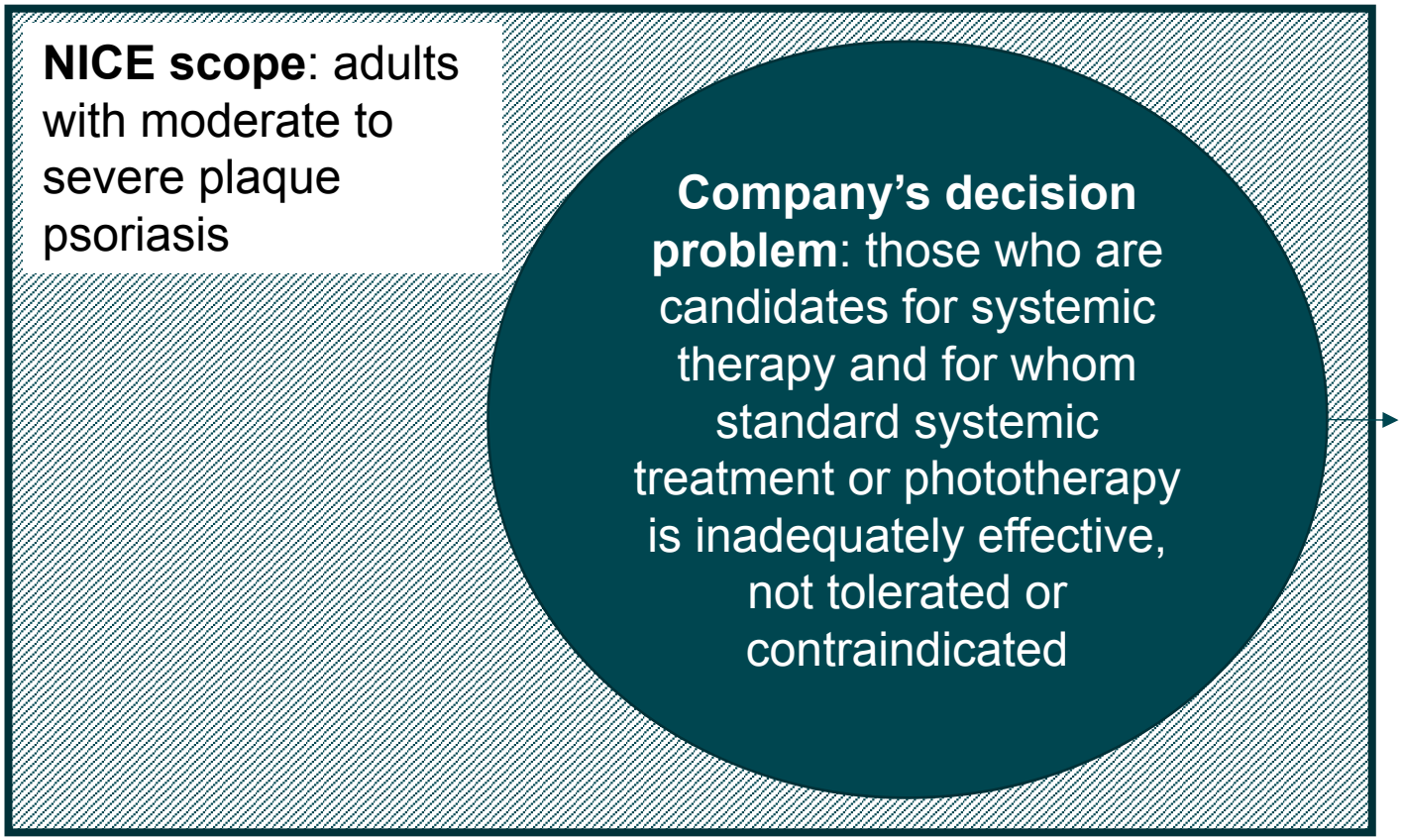
Clinical perspective

Provides another treatment option for psoriasis that has not responded to existing therapies

- Very effective but available evidence is only from clinical trials
- An alternative interleukin-17 inhibitor with a different mode of action
- Administered as most other biological therapies so will have limited impact on NHS resources
- Safety profile comparable with other interleukin-17 inhibitors with candida infections being the most common known side effect
- Psoriasis Area and Severity Index (PASI)
  - dependent on affected body surface area and is not sensitive for people with localised disease at high impact sites who are unlikely to achieve NICE threshold for severe disease at PASI ≥10
  - Varying perspectives of minimal clinically importance difference: PASI 75 vs PASI 90

Decision problem – population and comparators

Company focus on narrower population compared with NICE scope to reflect likely position of brodalumab in NHS clinical practice



Comparators in company's decision problem:

- tumour necrosis factor-alpha inhibitors
- apremilast
- dimethyl fumarate
- ixekizumab
- secukinumab
- ustekinumab
- best supportive care

ERG: company's decision problem appropriate and reflects likely position of brodalumab in NHS clinical practice and treatment options at that stage; but 17-35% of patients in AMAGINE did not have prior systemic therapy or phototherapy

Decision problem – outcomes

Company submission does not include symptoms on face and relapse rates

NICE scope and Company submission

- severity of psoriasis (including the Psoriasis Area and Severity Index [PASI])
- psoriasis symptoms on the face, scalp and nails
- mortality
- response rate
- relapse rate
- adverse effects of treatment
- health-related quality of life (including dermatology life quality index [DLQI])

Company submission: states that outcomes are included as per NICE scope

ERG comments

- Outcome measures and assessment time points are appropriate
- Symptoms on face and relapse rates not presented in company submission
- No relapse rates presented so it is impossible to know whether patients achieving PASI response at the end of induction (12 weeks) maintained their response or stopped responding, or if patients responded only after the initial 12 week treatment period

Decision problem – subgroups

Company submission includes subgroups based on severity of disease, history and response to previous treatments, concomitant use of topical treatment and baseline demographics

NICE scope	Company submission
• previous use of non-biologics • previous use of biologics • severity of psoriasis (moderate, severe)	• severity of psoriasis (PASI <20 or ≥20; DLQI ≤10 or >10) • previous use of non-biologics or phototherapy • previous use of non-biologics • number of previous non-biologics (0, 1 or ≥2) • non-biologics failure or contraindication • previous use of biologics • previous failure of biologics • previous use of anti-TNF therapy • concomitant use of topical therapy • baseline total body weight (≤100kg or >100kg) • geographic region • age (<65 or ≥65 years) • sex
Company rationale	
Additional subgroups of potential relevance were included	

DLQIDermatology Life Quality Index, PASIPsoriasis Area and Severity Index

Clinical evidence

3 Phase 3 randomised controlled trials with open-label extension for all studies

- AMAGINE-1 (brodalumab 140mg and 210mg, placebo)
- AMAGINE-2 and -3 (brodalumab 140mg and 210mg, ustekinumab 45 or 90mg, placebo) – identical in design

– only results of licensed brodalumab [210mg every 2 weeks] in company submission

– results from open-label extension of all trials excluded from health economic model

Network meta-analysis

brodalumab, apremilast, dimethyl fumarate, fumaric acid esters, biologics (*adalimumab, etanercept, infliximab, ixekizumab, secukinumab, ustekinumab*) and common comparators (*placebo, acitretin, methotrexate*)

Outcomes measures – sPGA and EQ-5D-3L

Severity of psoriasis

Static Physician Global Assessment (sPGA)

- measure physician's impression of patient's psoriasis based on severity of induration, scaling and erythema
- score: 0 (clear), 1 (almost clear) to 5 (severe)

Health-related quality of life

EuroQol-5 Dimension-3L (EQ-5D-3L)

- generic preference based measure of health outcome
- used to calculate utility score based on a descriptive profile or a health state
- EQ-5D-3L data collected from AMAGINE-1 using UK preference weights

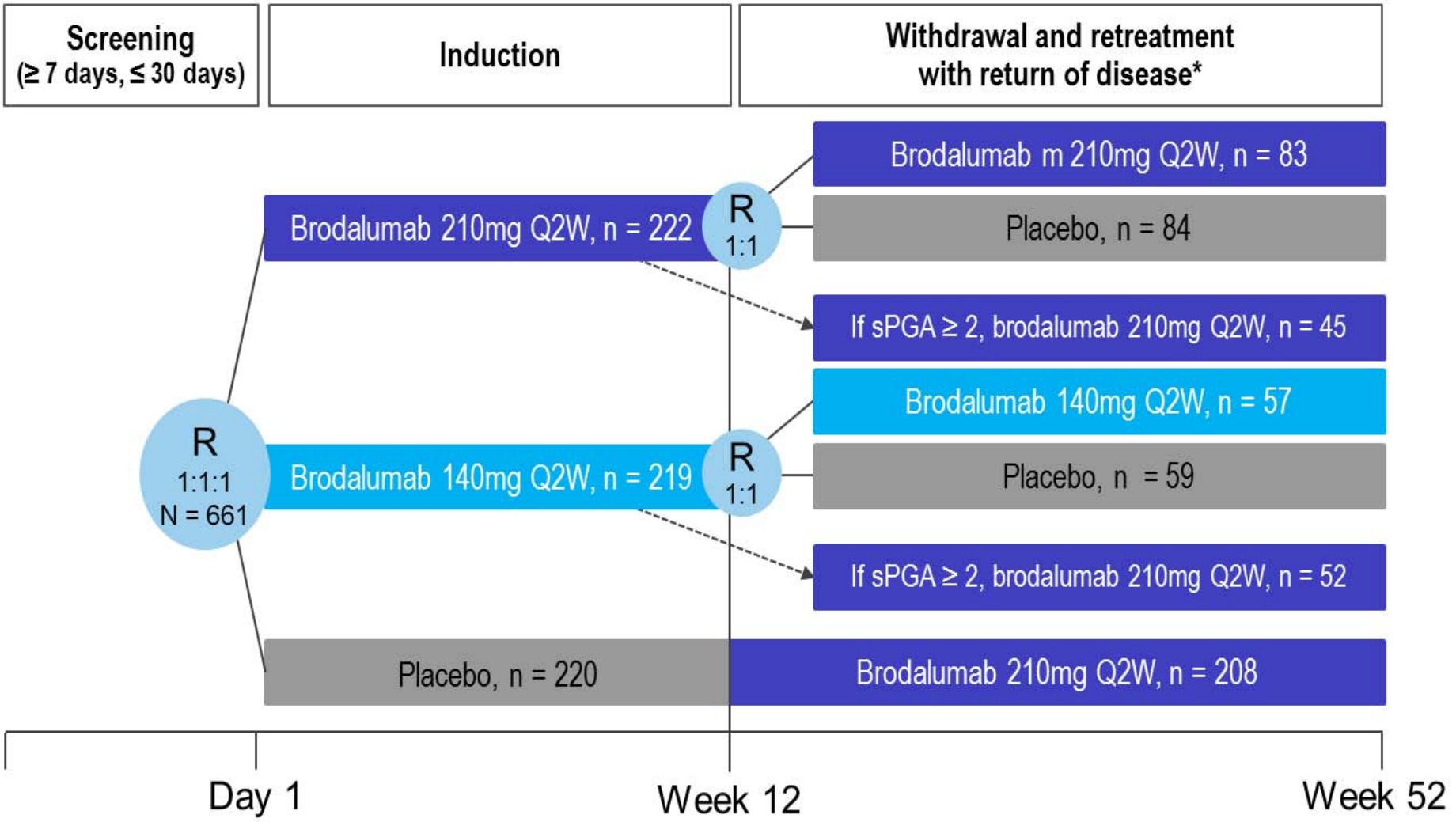
AMAGINE trials

Studies only included people with stable plaque psoriasis (PASI ≥12) and did not include any UK centres

Design	Phase 3, multicentre **(no UK sites)**, stratified randomised (interactive voice response system), double-blind, parallel group, 12 week induction, 40 week maintenance and open-label extension (ended early on 22/05/2015)
Location	AMAGINE-1: Canada, Europe, USA (73 sites) AMAGINE-2 and -3: Australia, Canada, Europe, USA (142 sites)
Population	Adults (18 to 75 years) with **stable moderate to severe** plaque psoriasis for at least 6 months **(PASI ≥12, sPGA ≥3, body surface area involvement ≥10%)**, eligible for biological therapy Patients not excluded because of increased risk of suicidal ideation and behaviour or psoriatic arthritis
Intervention*	Brodalumab 210mg at weeks 0, 1, 2, 4, 6, 8 and 10 **(7 doses)**
Comparators	All trials: placebo AMAGINE-2 and -3: ustekinumab 45 or 90mg at weeks 0, 4, every 12 weeks
Outcomes	Co-primary endpoints vs placebo: PASI 75 and sPGA 0 or 1 at 12 weeks Endpoint vs ustekinumab: PASI 100 at 12 weeks **Other outcomes (all trials):** PASI 90, PASI 100, sPGA 0, DLQI, PSI AMAGINE-1: PSSI (scalp involvement), EQ-5D-3L, HADS AMAGINE-2 and -3: NAPSI (nail involvement)

*Information on brodalumab 140mg not included

AMAGINE-1 trial design



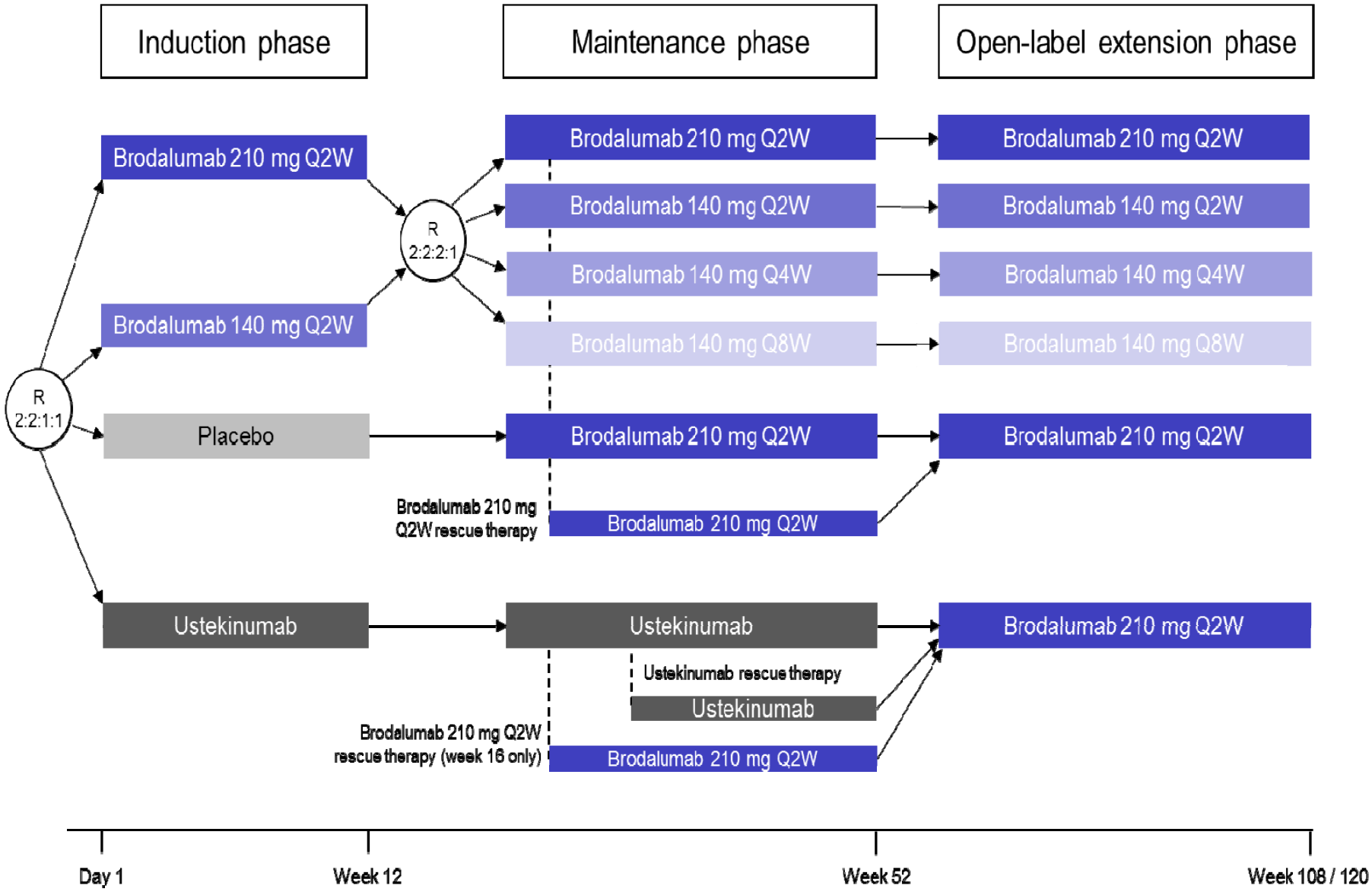
AMAGINE-1 trial design

After 12 week induction, depending on treatment response, patients on brodalumab are re-randomised to continue brodalumab or receive placebo (can receive brodalumab rescue therapy if symptoms returned)

Induction (12 weeks) Randomised[a] 1:1:1 to:	Maintenance (40 weeks)	Open-label extension (from 52 to 120 weeks)
Brodalumab 210mg Q2W (n=222)[b]	**sPGA 0 or 1**: re-randomised[c] 1:1 to: • brodalumab 210mg Q2W (n=83) • placebo[d] (n=84) **sPGA ≥2**: brodalumab 210mg Q2W (n=45)	Continued at same brodalumab maintenance or rescue dose
Brodalumab 140mg Q2W (n=219)[b]	**sPGA 0 or 1**: re-randomised[c] 1:1 to: • brodalumab 140mg Q2W (n=57) • placebo[d] (n=59) **sPGA ≥2**: brodalumab 210mg Q2W (n=52)	
Placebo (n=220)	Received brodalumab 210mg Q2W (n=208)	Continued at same brodalumab dose

[a]Randomisation stratified for geographic region, baseline body weight (≤100 or >100kg) and prior use of biologics. Inclusion of patients with previous biologic use was capped at 50% of the study population
[b]Patients receive treatment in maintenance phase depending on sPGA score
[c]Re-randomisation stratified for week 12 body weight (≤100 or >100kg), week 12 treatment response (sPGA 0 or ≥1), induction regimen
[d]Patients re-randomised to placebo whose psoriasis worsened (sPGA ≥3) between weeks 16 and 52, received rescue therapy of induction brodalumab dose
sPGA Static Physician Global Assessment, Q2W Every 2 weeks

AMAGINE-2 and -3 trial design



AMAGINE-2 and -3 trial design

After 12 week induction, patients on brodalumab are re-randomised to 4 doses of brodalumab. During the maintenance phase, patients could receive rescue therapy

Induction (12 weeks) Randomised[a] 2:2:1:1 to:	Maintenance (40 weeks)*	Open-label extension (from 52 to 120 weeks for AMAGINE-2 and 108 weeks for AMAGINE-3)
Brodalumab 210mg Q2W (n_2=612, n_3=624)	Re-randomised[b] 2:2:2:1 to brodalumab: 210mg Q2W (n_2=334, n_3=342) 140mg Q2W (n_2=337, n_3=343) 140mg Q4W (n_2=335, n_3=341) 140mg Q8W (n_2=168, n_3=174)	Continued at same brodalumab dose
Brodalumab 140mg Q2W (n_2=610, n_3=629)		
Ustekinumab 45 or 90mg (n_2=300, n_3=313)	Continued at same ustekinumab dose (n_2=289, n_3=301)	Received brodalumab 210mg Q2W
Placebo (n_2=309, n_3=313)	Received brodalumab 210mg Q2W (n_2=297, n_3=298)	Continued at same brodalumab dose

[a]Randomisation stratified for geographic region, baseline weight (≤100 or >100kg) and prior use of biologics
[b]Re-randomisation stratified for week 12 weight (≤100 or >100kg), week 12 treatment response (sPGA 0 or ≥1), induction regimen
n_2Number of patients in AMAGINE-2, n_3Number of patients in AMAGINE-3, ^{QnW}Every n weeks e.g. Q2W
***Patients with inadequate response receive rescue therapy (blinded) at week 16 regardless of treatment arm.** After week 16 and before week 52, brodalumab groups receive brodalumab 210mg Q2W and ustekinumab group continue to receive ustekinumab.

AMAGINE trials – ERG comments

- Quality assessment
  - 3 good quality trials with low risk of bias
  - results likely to be reliable
- Re-randomisation design and efficacy analysis set
  - cohorts at week 52 differ from week 12
  - PASI 75 response rates provide limited information on maintenance of treatment response
  - at week 52, many patients had discontinued (some because of lack of response) and all were imputed as non-responders (completed: 87% AMAGINE-2, 88% AMAGINE-3)
- Discontinuation rates at 52 weeks for brodalumab (210mg every 2 weeks) were low (completed: 81 to 82%)
  - proportions are comparable with drug survival rates published for other biologics

Baseline characteristics – demographics

ERG: baseline characteristics across different treatment groups in AMAGINE trials are similar

	Age (mean ± SD) in years	% men	% white	Body weight (mean ± SD) in kg	BMI (mean ± SD) in kg/m²
AMAGINE-1					
Brodalumab* (n=222)	46 ± 12	73	91	91.4 ± 23.4	31.0 ± 7.7
Placebo (n=220)	47 ± 13	73	92	90.4 ± 20.1	30.3 ± 6.6
AMAGINE-2					
Brodalumab* (n=612)	45 ± 13	69	90	91 ± 23	30.5 ± 7.2
Ustekinumab (n=300)	45 ± 13	68	90	91 ± 24	30.6 ± 7.1
Placebo (n=309)	44 ± 13	71	88	92 ± 23	30.5 ± 7.0
AMAGINE-3					
Brodalumab* (n=624)	45 ± 13	69	91	90 ± 23	30.3 ± 7.3
Ustekinumab (n=313)	45 ± 13	68	90	90 ± 22	30.4 ± 6.8
Placebo (n=315)	44 ± 13	66	93	89 ± 22	29.9 ± 6.7

*210mg every 2 weeks, [BMI]Body mass index, [n]Number of patients, [SD]Standard deviation

Baseline characteristics – psoriasis severity

Average PASI and DLQI scores in AMAGINE trials are [redacted] than the definition used in previous NICE appraisals for severe psoriasis (PASI ≥10 and DLQI >10)

	PASI[a,b,c]	DLQI[a,b]	BSA[a]	PSI[a]	% sPGA =		
					3	4	5
AMAGINE-1							
Brodalumab* (n=222)	19.4 ± 6.6	14.2 ± 7.3	25.1 ± 15.3	18.9 ± 6.7	55	39	6
Placebo (n=220)	19.7 ± 7.7	13.9 ± 6.8	26.9 ± 17.1	19.0 ± 6.7	52	41	7
AMAGINE-2							
Brodalumab* (n=612)	20.3 ± 8.3	[redacted]	26 ± 16	18.6 ± 6.8	52	42	7
Ustekinumab (n=300)	20.0 ± 8.4	[redacted]	27 ± 19	18.9 ± 7.0	51	44	5
Placebo (n=309)	20.4 ± 8.2	[redacted]	28 ± 17	18.6 ± 7.1	54	39	7
AMAGINE-3							
Brodalumab* (n=624)	20.4 ± 8.3	[redacted]	28 ± 18	18.7 ± 7.2	60	36	4
Ustekinumab (n=313)	20.1 ± 8.4	[redacted]	28 ± 18	18.7 ± 6.8	61	33	6
Placebo (n=315)	20.1 ± 8.7	[redacted]	28 ± 17	19.0 ± 6.7	61	36	3

*210mg every 2 weeks, [a]Mean ± standard deviation, [b]**Previous NICE appraisals severe definition: PASI ≥10 & DLQI >10**, [c]PASI inclusion criterion in AMAGINE trials were ≥12

Higher scores indicate more severe disease or greater burden. [BSA]Percentage of body surface area affected, [DLQI]Dermatology Life Quality Index (0-30), [n]Number of patients, [PASI]Psoriasis Area and Severity Index (0-72), [PSI]Psoriasis Symptom Inventory (0-32), [sPGA]Static Physician Global Assessment (3=moderate, 4=severe, 5=very severe)

Baseline characteristics – psoriasis and previous treatment

AMAGINE-1 patients had psoriasis for longer and larger proportions had psoriasis arthritis and previous treatments than AMAGINE-2 and -3

	% on previous systemic therapy or phototherapy	% on previous biological therapy	Duration of psoriasis (mean ± SD) in years	% Psoriatic arthritis
AMAGINE-1				
Brodalumab* (n=222)	81	47	20 ± 13	26
Placebo (n=220)	83	46	21 ± 12	29
AMAGINE-2				
Brodalumab* (n=612)	77	29	19 ± 12	19
Ustekinumab (n=300)	75	28	19 ± 13	17
Placebo (n=309)	74	29	18 ± 12	17
AMAGINE-3				
Brodalumab* (n=624)	68	25	18 ± 12	20
Ustekinumab (n=313)	70	24	18 ± 12	20
Placebo (n=315)	65	24	18 ± 12	19

*210mg every 2 weeks, [n]Number of patients, [SD]Standard deviation

Generalisability of AMAGINE population

Company concluded that AMAGINE population is similar to BADBIR registry population (UK and Ireland)

- Mean age in AMAGINE was similar to BADBIR (British Association of Dermatologists Biologic Interventions Register) registry population
- Company suggests that AMAGINE population is realistic because patients were not excluded on the basis of:
  - known cardiovascular disease (except myocardial infarction or unstable angina in previous 12 months)
  - psychiatric disorders or substance abuse (22% in BADBIR had depression)
  - previous psoriasis therapy

	AMAGINE	BADBIR
% men	69 to 73	59
Mean body weight (kg)	90 to 91	90
Mean body mass index (kg/m^2)	30 to 31	31
Mean duration of psoriasis (years)	18 to 20	23
% psoriatic arthritis	19 to 27	23

Generalisability of results from AMAGINE trials to NHS patients – ERG comments

- No UK sites were included in AMAGINE
  - different treatment sequencing or drug availability in trial countries may make AMAGINE population less generalisable to UK setting
- Disease severity definitions are different in AMAGINE and previous NICE appraisals
  - AMAGINE: PASI ≥12 and mean baseline DLQI [redacted]
  - Previous NICE appraisals: PASI ≥10 and DLQI >10
- Age restriction (up to 75 years) in AMAGINE
  - ERG clinical advisor: older patients are usually more ill than general psoriasis population
- AMAGINE included patients with stable psoriasis
  - NHS patients eligible for brodalumab likely to have more severe or difficult to treat psoriasis, and may be less responsive to treatment than seen in AMAGINE
- 17-35% patients in AMAGINE had no previous systemic treatment or phototherapy and AMAGINE excluded patients on previous ustekinumab or anti-interleukin-17 therapy
  - inconsistent with proposed positioning of brodalumab

Induction key results at 12 weeks (full analysis set, non-responder imputation)

For all outcomes, brodalumab was significantly more effective than placebo and ustekinumab

ERG: PASI 75 response rates in placebo groups were different across AMAGINE trials

	% PASI response (95% CI)			% sPGA (95% CI)	% DLQI (95% CI)[b]
	PASI 75	**PASI 90**	**PASI 100**	**0 or 1**	**0 or 1**
AMAGINE-1					
Brodalumab (n=222)[a]	83 (78, 88)	NR	42 (35, 49)	76 (70, 81)	56 (NR)
Placebo (n=220)	**3 (1, 6)**	NR	0.5 (0, 3)	1 (0, 4)	5 (NR)
AMAGINE-2					
Brodalumab (n=612)[a]	***86 (83, 89)[c]***	***70 ([redacted])***	***44 (41, 49)***	***79 (75, 82)***	61 ([redacted])
Ustekinumab (n=300)	70 (65, 75)	47 ([redacted])	22 (17, 27)	61 (55, 67)	44 ([redacted])
Placebo (n=309)	**8 (5, 12)**	3*	1 (0, 2)	4 (2, 7)	4.5 (NR)
AMAGINE-3					
Brodalumab (n=624)[a]	***85 (82, 88)***	***69 ([redacted])***	***37 (33, 41)***	***80 (76, 83)***	59 ([redacted])
Ustekinumab (n=313)	69 (64, 74)	48 ([redacted])	19 (14, 23)	57 (52, 63)	44 ([redacted])
Placebo (n=315)	**6 (4, 9)**	2*	0.3 (0, 2)	4 (2, 7)	7 (NR)

For all outcomes, brodalumab vs placebo: statistically significant (p<0.001); comparative results not reported for PASI 90; *Data taken from Figure 7 (company submission, page 47) – confidence intervals not reported. ***Brodalumab vs ustekinumab: statistically significant (p<0.01).*** [a]Brodalumab 210mg Q2W, [b]Proportion of patients scoring 0 or 1 in DLQI at baseline ranged from [redacted], [c]Company factual accuracy check clarified p<0.001 brodalumab vs ustekinumab, [CI]Confidence intervals, [DLQI]Dermatology Life Quality Index, [n]Number of patients, [NR]Not reported, [PASI]Psoriasis Area and Severity Index, [sPGA]Static Physician Global Assessment (0=clear, 1=almost clear)

Time to response during induction (full analysis set, as observed)

Brodalumab significantly decreased the median time to PASI 75 response compared to ustekinumab

	Median time (95% CI) to PASI response in weeks	
	PASI 90*	**PASI 75**
AMAGINE-1		
Brodalumab	6.3	NR
Placebo	NR	NR
AMAGINE-2		
Brodalumab[a]	[redacted], n=NR	**4.1** (not estimable), n=556
Ustekinumab	[redacted], n=NR	8.1 (8.0, 8.3), n=228
AMAGINE-3		
Brodalumab[a]	[redacted], n=NR	**4.1** (4.1, 4.3), n=568
Ustekinumab	[redacted], n=NR	8.1 (8.1, 9.9), n=229)

Brodalumab vs ustekinumab: statistically significant (p<0.001)

[a]Brodalumab 210mg every 2 weeks, *number of patients in each group not reported

[CI]Confidence intervals, [n]Number of patients, [NR]Not reported, [PASI]Psoriasis Area and Severity Index

EQ-5D-3L utility scores at week 12 (full analysis set, multiple imputation) – AMAGINE-1

Placebo n=216, Brodalumab 210mg Q2W n=221

Outcomes measures – PSSI and NAPSI

Psoriasis symptoms on the face, scalp and nails

Psoriasis Scalp Severity Index (PSSI)

- modified version of Psoriasis Area and Severity Index for the scalp
- assesses extent of involvement and severity of erythema, induration and desquamation
- score: 0 (no psoriasis) to 72 (most severe disease)
- PSSI XX: relative reduction in PSSI score from baseline
- PSSI 75 = 75% improvement from baseline

Nail Psoriasis Severity Index (NAPSI)

- divide nail into 4 quadrants
- assess presence of signs in nail matrix (pitting, leukonychia, red spots in lunula and crumbling) and nail bed (onycholysis, oil drop dyschromia, splinter haemorrhages and hyperkeratosis)
- assess severity by area of involvement (0=not present to 4=present in all quadrants; total score for each nail is 0-32)
- total NAPSI score = sum of the overall scores of all involved fingernails

Psoriasis Scalp Severity Index at week 12 (PSSI 75; full analysis set) – AMAGINE-1

Brodalumab [redacted] *compared to placebo*

- [redacted] of patients in AMAGINE-1 (n= [redacted]) had scalp involvement (baseline PSSI score ≥15

†Brodalumab 210mg every 2 weeks vs placebo: [redacted] for patients achieving 75% improvement in PSSI compared to baseline

Nail Psoriasis Severity Index at 12 weeks (NAPSI; full analysis set, multiple imputation) – AMAGINE-2 and -3

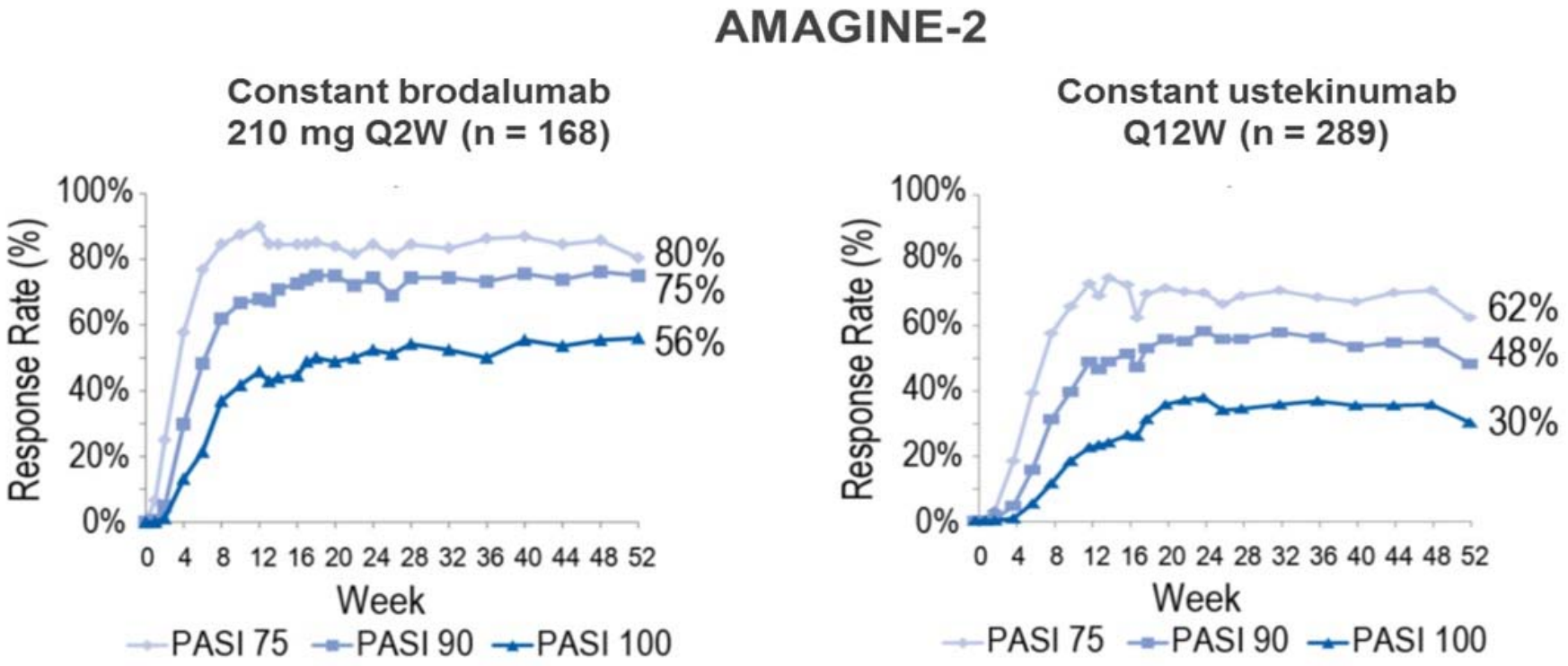
Brodalumab is [redacted] compared to placebo

[redacted] of patients in AMAGINE-2 and -3 (n=[redacted]) had nail involvement (baseline NAPSI score ≥6)

†Brodalumab 210mg every 2 weeks vs placebo: [redacted]
Brodalumab vs ustekinumab: p value not calculated

Treatment waning: maintenance of PASI response at 52 weeks (efficacy analysis set, non-responder imputation) – AMAGINE-2

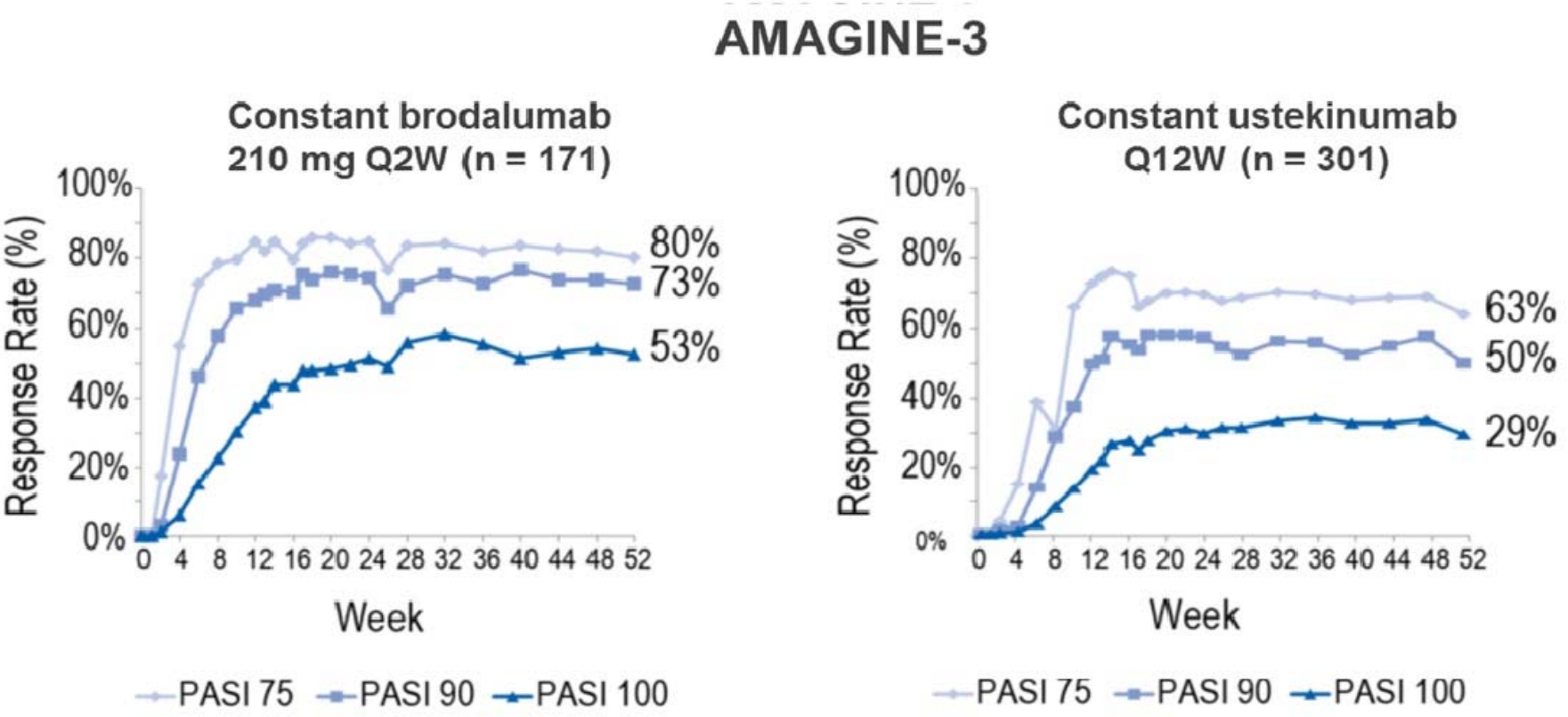
PASI response rates are largely maintained after 12 weeks up to 52 weeks in patients receiving brodalumab (210mg every 2 weeks) during induction and maintenance phases compared with ustekinumab



ERG: Numbers in Figure and text are inconsistent; reasons unclear

Treatment waning: maintenance of PASI response at 52 weeks (efficacy analysis set, non-responder imputation) – AMAGINE-3

PASI response rates are largely maintained after 12 weeks up to 52 weeks in patients receiving brodalumab (210mg every 2 weeks) during induction and maintenance phases compared with ustekinumab



ERG: Numbers in Figure and text are inconsistent; reasons unclear

Maintenance key results at 52 weeks (non-responder imputation)

For all outcomes, brodalumab had [redacted] than placebo and ustekinumab

	% PASI response (95% CI)			% sPGA (95% CI)	% DLQI (95% CI)
	PASI 75	PASI 90	PASI 100	0 or 1	0 or 1
AMAGINE-1[a] (full analysis set)					
Brodalumab (n=83)	[redacted]	78 (NR)	67 (NR)	83 (NR)	NR
Placebo (n=84)	0 (NR)	0 (NR)	0 (NR)	0 (NR)	NR
AMAGINE-2 (efficacy analysis set)					
Brodalumab (n=334)[b]	[redacted]	[redacted]	[redacted]	63 (57, 68)	[redacted]
Ustekinumab (n=289)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AMAGINE-3 (efficacy analysis set)					
Brodalumab (n=342)[b]	[redacted]	[redacted]	[redacted]	61 (55, 60)	[redacted]
Ustekinumab (n=301)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Patients receiving brodalumab 210mg during induction and had a sPGA of 0 or 1 at week 12 were re-randomised to brodalumab 210mg or placebo, [b]Patients receiving brodalumab (140mg or 210mg) during induction were re-randomised at week 12 to 4 brodalumab doses. Results presented for patients re-randomised to only brodalumab 210mg every 2 weeks at week 12, [c]Patients receiving ustekinumab during induction continued at same dose during maintenance, Brodalumab vs placebo: adjusted p value <0.001, *Data taken from Figure 17 (company submission, page 56), [CI]Confidence intervals, [n]Number of patients, [NR]Not reported, [PASI]Psoriasis Area and Severity Index, [sPGA]Static Physician Global Assessment (0=clear, 1=almost clear)

CONFIDENTIAL

Open-label extension results (as observed) up to 120 weeks

For all outcomes, [redacted] with brodalumab

Brodalumab 210mg every 2 weeks	% PASI response			% sPGA
	75	90	100	0 or 1
AMAGINE-1 (excludes patients on placebo or brodalumab 140mg Q2W during maintenance)				
52 weeks (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
120 weeks (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
AMAGINE-2 (excludes patients on lower brodalumab doses or ustekinumab during maintenance)				
52 weeks (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
120 weeks (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
AMAGINE-3 (excludes patients on lower brodalumab doses or ustekinumab during maintenance)				
52 weeks (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]
108 weeks (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]

CONFIDENTIAL

Subgroup analyses

In PASI response rates, brodalumab was [redacted] *, regardless of disease severity or previous use of systemic therapy, phototherapy and biological therapy*

Company: provides evidence that brodalumab is effective regardless of previous therapies (assumption in economic model)

- Subgroup analyses used pooled population from AMAGINE 1, 2 and 3
  - [redacted]
  - In subgroups related to disease severity and prior therapy, for PASI 75, PASI 90 and PASI 100, brodalumab 210mg every 2 weeks was [redacted]
  - Significant differences were observed for baseline weight subgroup. Not relevant because weight based dosing is outside the license for brodalumab
- **ERG:** results added together from AMAGINE trials instead of using a weighted average of the studies

Adverse events (safety analysis set) during **maintenance**

ERG: brodalumab had higher rates of adverse events leading to discontinuation than ustekinumab in AMAGINE-2 and -3

Maintenance phase (up to 52 weeks)	Exposure-adjusted adverse event rate per 100 patient-years			
	Any[b]	Serious	Death	Leading to discontinuation from study or drug
AMAGINE-1				
Brodalumab (n=345)^	380	9.9	1.1	7
AMAGINE-2				
Brodalumab (n=486)[a,c]	403	10	0.3	8.4
Ustekinumab (n=300)[d]	413	13	0.8	5.3
AMAGINE-3				
Brodalumab[a] (n=489)	397	8	3.1	7
Ustekinumab (n=313)	376	4	1.6	4.4

^constant brodalumab 210mg Q2W, [a]**Patients receiving brodalumab (140mg or 210mg) during induction were re-randomised at week 12 to 210mg brodalumab, and placebo group at induction,** [b]Most common adverse events for all groups in AMAGINE trials were injection site reactions; mild or moderate *Candida* infections and neutropaenia occurred more frequently in brodalumab than other groups, [c]3 suicide attempts, [d]1 suicide attempt, [n]Number of patients

[redacted]

Suicidal ideation and behaviour (SIB)

ERG: FDA and EMA states that the relationship between brodalumab and SIB is inconclusive; warnings and precautions included in summary of product characteristics. AMAGINE did not exclude patients with higher risk of SIB

- Results up to open label extension (108 or 120 weeks):
  - 4 completed suicides (1 adjudicated as indeterminate), all after exposure to brodalumab ([redacted] days after last dose)
  - [redacted]
  - [redacted]
- Comparative analysis of apremilast, ixekizumab, secukinumab and brodalumab using regulatory data from US Food and Drug Administration done by Valeant Pharmaceuticals*
  - rates of completed suicides are consistent across all drugs
  - rates of attempted suicide in brodalumab is similar to ixekizumab (no completed suicides with ixekizumab)
  - observation time-adjusted patient incidence rate (per 100/patient-years) of suicide attempts higher in brodalumab (0.11, 95% CI 0.05 to 0.20) compared with external pooled estimate (0.04, 95% CI 0.01 to 0.10)

CIConfidence intervals, *US licensee of brodalumab

Network meta-analysis – included studies (base case)

Treatment	Studies
Brodalumab	AMAGINE-1, -2 and -3, Nakagawa 2016, Papp 2012
Apremilast	ESTEEM-1 and -2, LIBERATE, PSOR-005, Ohtsuki 2017, Papp 2013
Dimethyl fumarate	BRIDGE
Adalimumab	CHAMPION, REVEAL, VOYAGE-1 and -2, X-PLORE, Asahina 2010, Bissonnette 2013, Cai 2016, Goldminz 2015, Gordon 2006
Etanercept	ACCEPT, FIXTURE, LIBERATE, M10-315, PRISTINE, reSURFACE2, PIECE, Bagel 2012, Bachelez 2015, Caproni 2009, Gisondi 2008, Gottlieb 2003 and 2011, Leonardi 2003, Papp 2005, Tyring 2006, Van de Kerkhof 2008
Infliximab	EXPRESS, EXPRESS II, PIECE, RESTORE-1, SPIRIT, Chaudhari 2001, Torii 2010, Yang 2012
Ixekizumab	IXORA-S, UNCOVER -1, -2 and -3
Secukinumab	CLEAR, ERASURE, FEATURE, FIXTURE, JUNCTURE, SCULPTURE
Ustekinumab	ACCEPT, AMAGINE-2 and -3, CLEAR, IXORA-S, LOTUS, PEARL, PHOENIX-1 and -2, Igarashi 2012

Studies included other therapies (methotrexate, guselkumab, tofacitinib, briakinumab, tildrakizumab, fumaderm and acitretin)

Network meta-analysis – base case and sensitivity analyses

Base case: PASI response rates at induction

- 59 trials (n=28,346): moderate to severe plaque psoriasis, eligible for systemic therapy
- Licensed doses of therapies as in scope; induction differed for treatments:
  - 10 weeks: infliximab
  - 12 weeks: brodalumab, etanercept, ixekizumab, secukinumab, ustekinumab
  - 16 weeks: adalimumab, apremilast, dimethyl fumarate
- Unlicensed doses and conventional non-biologics: included if contribute to indirect evidence for relevant therapies
- Assumed: 2x etanercept 25mg per week = single 50mg weekly dose
- Omitted comparators: non-biologics, best supportive care

Sensitivity analyses

Sensitivity analysis 1: EMA licensed dose recommended by NICE included
Sensitivity analysis 2: 16 week outcomes from CLEAR used (primary endpoint of trial) vs 12-week outcomes used in base case
Sensitivity analysis 3: trials <100 patients randomised excluded
Sensitivity analysis 4: trials >30% randomised patients had previous biologics excluded (30% pragmatically chosen to include as many brodalumab trials as possible)
Sensitivity analysis 5: trials with mean baseline PASI >25 excluded

Network meta-analysis – assumptions

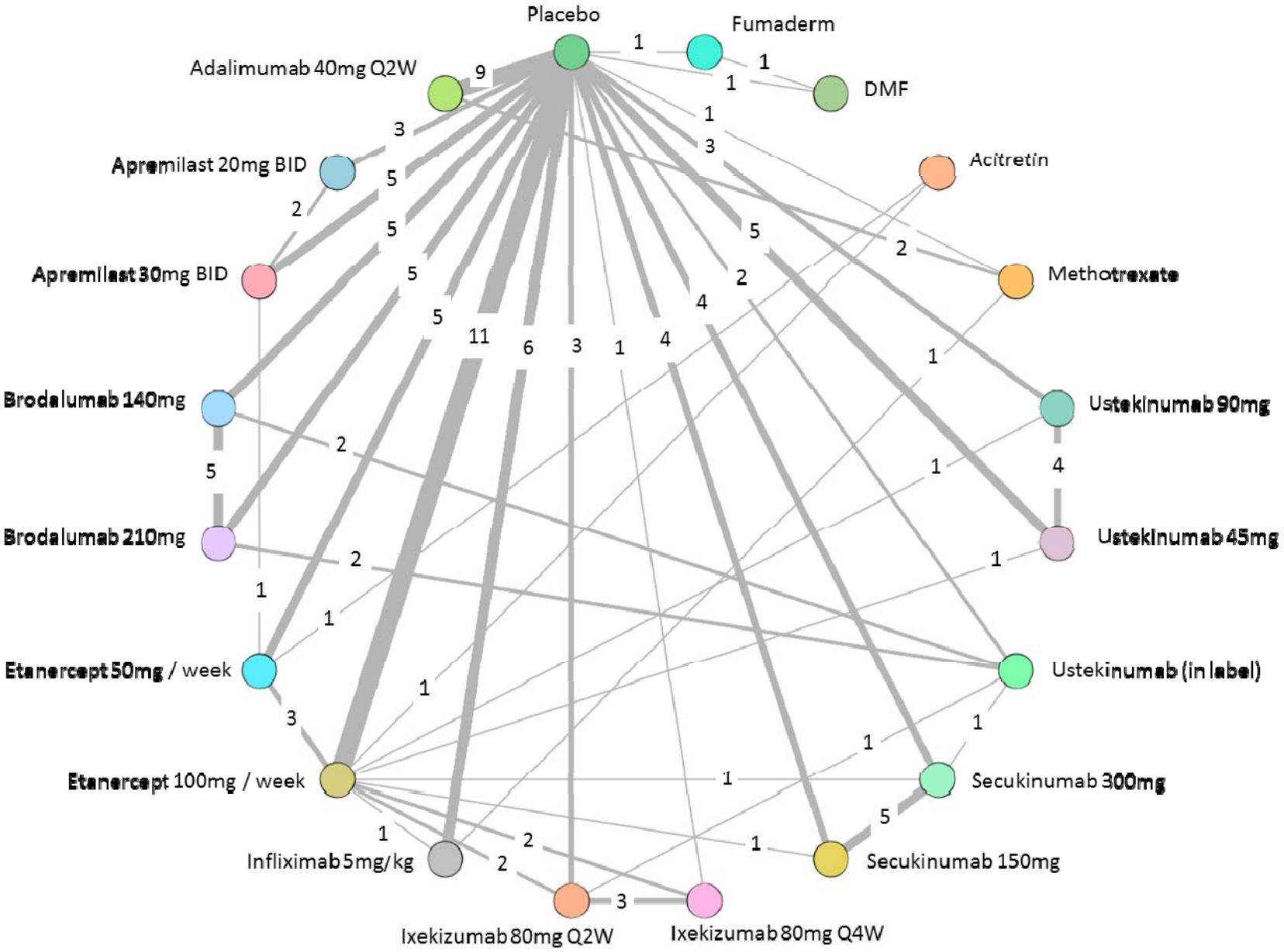
Placebo arms in trials differed in treatment response which may lead to biased results when comparisons are made across trials. Placebo-adjusted network meta-analysis reduced heterogeneity, but company ***preferred unadjusted model because of lower DIC value***

Assumption	Company assessment
Homogeneity	• Low heterogeneity across base case and sensitivity analyses (statistical assessment using tau) • Substantial variation in placebo arm response rates: bias outcomes in comparisons across trials → placebo adjusted and unadjusted models explored (see results below). Adjusted model reduces unexplained heterogeneity but unadjusted model fit is better because DIC approach penalises complex models
Similarity	Baseline patient characteristics in studies are largely similar
Inconsistency	Results consistent across base case and sensitivity analyses

Model diagnostic, mean (95% CrI)	Unadjusted model	Placebo-adjusted model
	Random effects	Random effects
Adjustment covariate	[redacted]	[redacted]
Tau	[redacted]	[redacted]
DIC	[redacted]	[redacted]
Total residual deviance	[redacted]	[redacted]

CrlCredible intervals, DICDeviance information criterion (lower values better), NANot available

Base case network diagram



Network meta-analysis – ERG comments

Network meta-analysis was well conducted, trials adequately similar to be pooled. AMAGINE population was different at baseline compared to other trials. Only PASI response rates presented

- Quality assessment
  - well conducted; all relevant trials included (generally high quality with low risk of bias) and adequately similar to be pooled
- Only PASI response rates were presented.
  - Recent British Association of Dermatologists' guidelines on biologics for psoriasis (April 2017) included network meta-analyses for DLQI and tolerability
    - DLQI results at 12-16 weeks: secukinumab ranked best, then infliximab, ixekizumab, ustekinumab, adalimumab, etanercept, methotrexate, placebo
    - tolerability results at 12-16 weeks: ustekinumab ranked best, then adalimumab, secukinumab, methotrexate, placebo, etanercept, ixekizumab, infliximab
- AMAGINE population is different compared to other trials at baseline: quality of life slightly poorer and higher proportion received previous biologics

DLQI Dermatology Life Quality Index, PASI Psoriasis Area and Severity Index

Placebo-adjusted model – ERG comments

Placebo-adjusted model reduces heterogeneity and is preferred because of significant variation in response rates of placebo groups across trials

- Significant variation in PASI response rates of placebo groups across 49 placebo-controlled trials. For example,
  - PASI 50 response rates: 5.1 to 33.3%
  - PASI 75 response rates: 0 to 20% (AMAGINE trials: 2.7% to 8.1%)
- Although results for placebo-adjusted and unadjusted models are consistent, **placebo-adjusted model is preferred** to ensure relative treatment outcomes across trials are not biased. It reduces:
  - unexplained heterogeneity (estimated reference arm adjustment coefficient, β is statistically significantly different from 0)
  - between-study heterogeneity (95% credible interval of random effect, τ is narrower)
  - total residual deviance is similar (mean of 1,066 unadjusted vs 1,067 placebo-adjusted)

CONFIDENTIAL

NMA results – company and ERG placebo-adjusted base case

Results for unadjusted and placebo-adjusted base case and sensitivity analyses are consistent

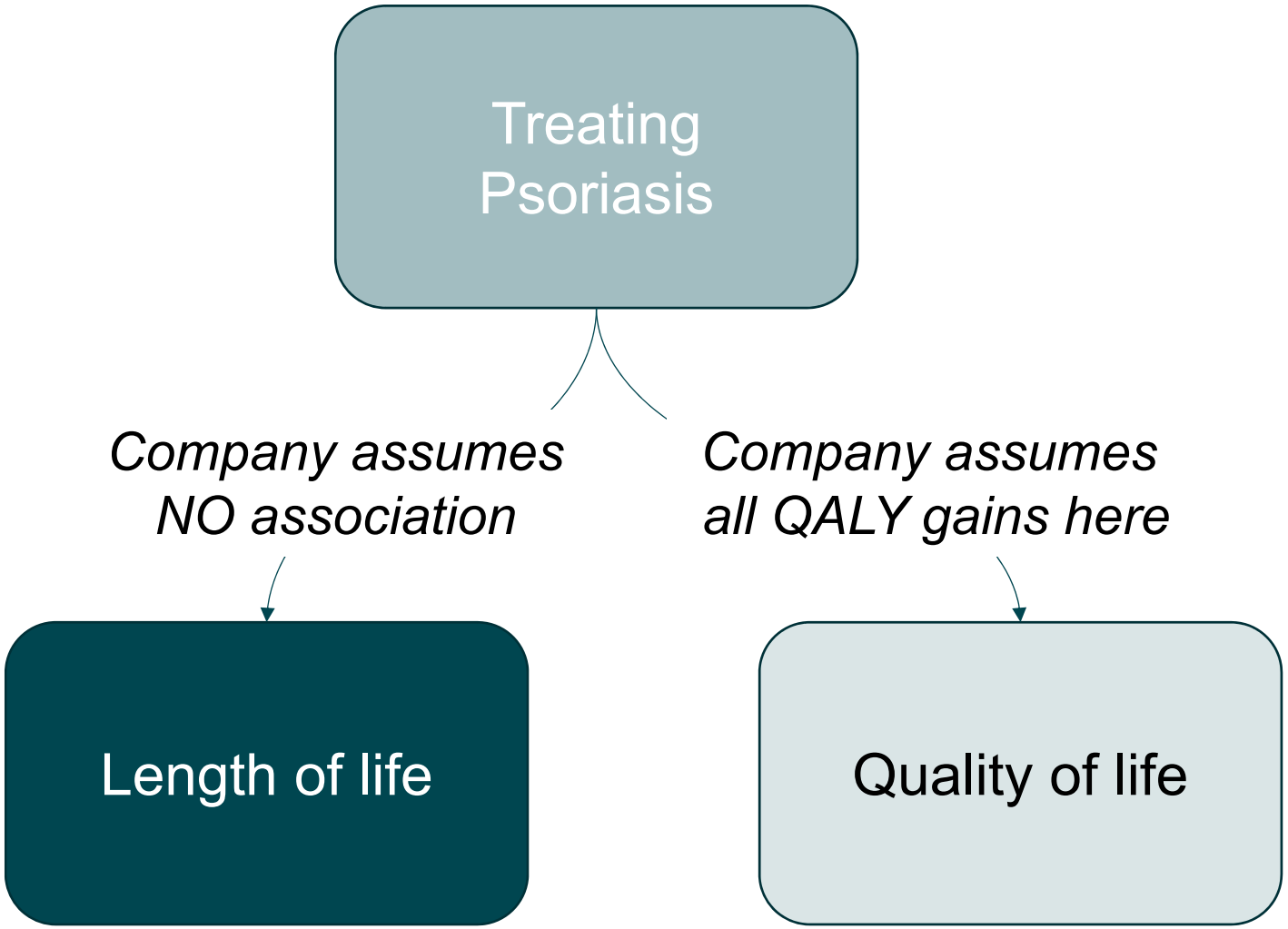
Treatment	Probability of PASI 75 response, median (95% CrI)				
	Base case (unadjusted)	Sensitivity analysis 1 (licensed doses)	Sensitivity analysis 4 (exclude studies >30% previous biologics)	Exclude phase 2 trials	ERG placebo-adjusted base case
Ixekizumab 80mg Q2W	90.4% (87, 93)	89.4% (85.2, 92.7)	90.9% (86.9, 93.8)	89.7% (86, 92.7)	89.1% (86.6, 91.2)
Brodalumab 210mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300mg	83.6% (79, 87.7)	83.4% (78.2, 87.9)	84% (78.9, 88.3)	82.8% (77.6, 87.2)	81.8% (78.5, 84.9)
Infliximab 5mg/kg	79.2% (72.8, 84.7)	82.6% (75.5, 88.3)	80.6% (73.8, 86.6)	78.9% (71.6, 85.1)	78.9% (75.0, 82.5)
Ustekinumab 45mg	71.6% (65.5, 77.1)	72.9% (66, 78.9)	69.9% (61.6, 77.4)	70.4% (63.7, 76.4)	69.7% (65.6, 73.7)
Ustekinumab 90mg	75.3% (69.3, 80.7)	76.9% (70, 82.7)	74.8% (65.6, 82.6)	74.3% (67.6, 80.2)	72.5% (68.0, 76.8)
Ustekinumab (in-label dose)	71% (64.7, 76.8)	70.2% (63.5, 76.4)	71% (64.1, 77.4)	69.4% (62.5, 75.8)	70.6% (66.2, 75.0)
Adalimumab 40mg Q2W	66% (59.3, 72.1)	63.4% (56.3, 70.1)	67.3% (60.1, 73.8)	64.5% (57.1, 71.2)	69.5% (65.6, 73.0)
Etanercept 50mg / week	39.1% (32.5, 46.2)	41.2% (33.4, 49.5)	40.5% (33.3, 48.1)	37.3% (30.3, 44.9)	39% (34.4, 43.8)
Apremilast 30mg BID	27.3% (21.5, 33.7)	26.8% (20.7, 33.5)	29.2% (22.4, 36.8)	26.6% (19.9, 34.2)	31.5% (27.1, 36.2)
Dimethyl fumarate	19.3% (11.4, 29.9)	18.7% (10.9, 29.3)	20.4% (12, 31.8)	18.7% (10.7, 29.5)	30.2% (21.8, 39.7)
Placebo	5.7% (4.6, 7.1)	5.5% (4.3, 6.9)	6.3% (4.9, 7.9)	5.4% (4.3, 6.8)	5.7% (4.6, 7.0)

NMA results – ERG placebo adjusted model (clinical effectiveness inputs)

Treatment	Median probability of PASI response				Ranking
	PASI 50	PASI 75	PASI 90	PASI100	
Ixekizumab (80 mg Q2W)	96.1%	89.1%	71.5%	41.1%	1
Brodalumab (210 mg)	[redacted]	[redacted]	[redacted]	[redacted]	2
Secukinumab (300 mg)	92.5%	81.8%	59.7%	29.2%	3
Infliximab (5 mg/kg)	90.9%	78.9%	55.6%	25.7%	4
Ustekinumab (90 mg)	87.0%	72.5%	47.4%	19.5%	5
Ustekinumab (in-label dose)	85.8%	70.6%	45.2%	18.1%	6
Ustekinumab (45 mg)	85.2%	69.7%	44.2%	17.4%	7
Adalimumab (40 mg)	85.0%	69.5%	43.9%	17.2%	8
Etanercept (100 mg/week)	71.2%	51.2%	26.4%	7.7%	9
Etanercept (50 mg/week)	59.8%	39.0%	17.3%	4.1%	10
Apremilast (30 mg)	51.9%	31.5%	12.6%	2.6%	11
Dimethyl fumarate	50.4%	30.2%	11.9%	2.4%	12
Placebo	14.7%	5.7%	1.3%	0.1%	13

Cost effectiveness

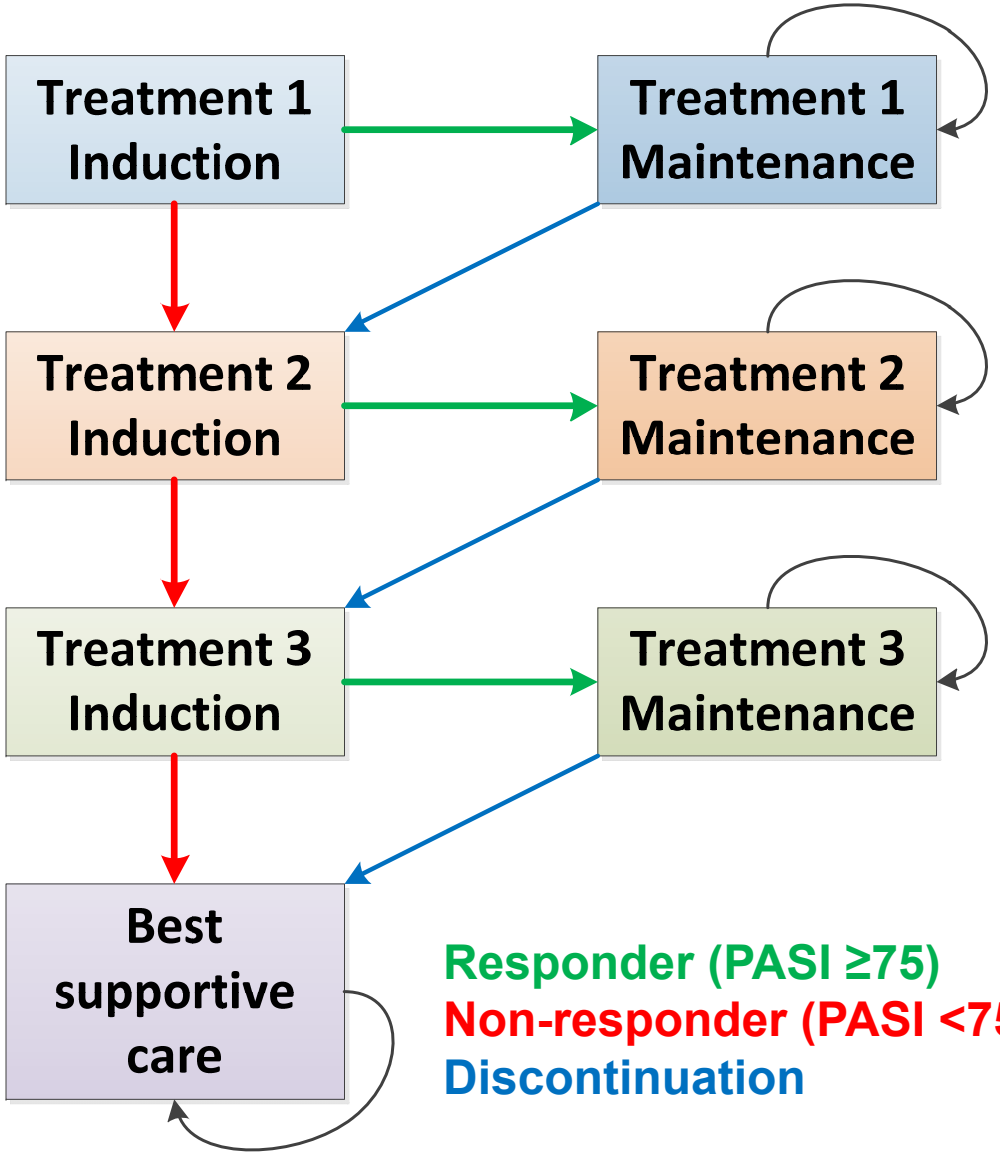
QALY gains – conceptual model

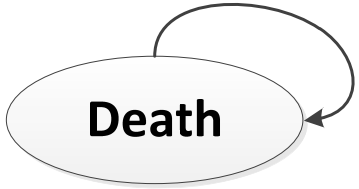


Increase in QALYs comes only from improvement in quality of life, rather than increasing length of life

Company model

ERG: model meets requirements of NICE reference case; high quality; similar to recent technology appraisals





NHS/PSS
3.5% discount

- Markov state transition model
- 40 year time horizon
- 2 week cycle length
- 3 treatment-related health states and death
- 9 treatment sequences
- Treatment-specific induction periods (10, 12 or 16 weeks)
- Responders constant annual discontinuation rate: 18.7%
- Baseline characteristics (similar to trials in network meta-analysis and AMAGINE): 45 years, mean weight 85.8kg, 68% men
- Serious adverse events (infections) modelled

PASI Psoriasis Area and Severity Index

Induction health state, transition probabilities and clinical effectiveness inputs

Induction: patients on drug for 10, 12 or 16 weeks (treatment specific)

- **End of induction:** patients split into 5 mutually exclusive PASI response levels (constant over time; from base-case network meta-analysis)
- **Responders (PASI ≥75):** continue drug in maintenance
- **Non-responders (PASI <75):** switch to next drug in sequence

Treatment	Induction period (weeks)	*Proportion of patients achieving:* PASI 0–49	PASI 50–74	PASI 75–89	PASI 90–99	PASI 100
Brodalumab	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	16	0.17	0.17	0.26	0.25	0.15
Apremilast	16	0.53	0.20	0.17	0.08	0.02
Dimethyl fumarate	16	0.63	0.17	0.13	0.05	0.01
Etanercept	12	0.40	0.20	0.21	0.14	0.05
Infliximab	10	0.09	0.12	0.23	0.30	0.26
Ixekizumab	12	0.03	0.06	0.17	0.30	0.44
Secukinumab	12	0.07	0.10	0.21	0.31	0.32
Ustekinumab[a]	16	0.14	0.15	0.25	0.27	0.18
BSC*	NA	0.85	0.09	0.04	0.01	0.00

[BSC]Best supportive care, [NA]Not applicable, [PASI]Psoriasis Area and Severity Index, [SE]Standard error; *response from placebo group in network meta-analysis; [a]based on weight-based dose (45 mg if patient weighs <100kg; 90 mg if >100 kg)

Maintenance health state, transition probabilities and discontinuation rates

Maintenance: patients on induction drug (same PASI response until discontinuation)

- Patients on all drugs **discontinue** at a constant annual rate of 18.7% (=0.79% 2-week cycle)*
- On discontinuation, patients return to baseline PASI (at start of induction) and switch to next drug in sequence or best supportive care (after 3rd drug)

*Rate based on discontinuation data in years 2 and 3 from BADBIR registry. Year 1 data excluded to avoid double counting of non-response already accounted for in trial data. Previous appraisals have used all 3 years giving an annual rate of 20%.

Scenario analysis: 7.3% for IL-inhibitors (brodalumab, ixekizumab, secukinumab and ustekinumab) vs 14.6% for anti-TNF therapies (adalimumab, etanercept and infliximab), apremilast and dimethyl fumarate. Based on BADBIR data showing lower discontinuation rate with ustekinumab (assumed same for all IL-inhibitors) than adalimumab (most common; used to represent all anti-TNF therapies, and apremilast/dimethyl fumarate that had no data).

ERG: company's base-case approach is reasonable, justifiable and consistent with other appraisals, but there is uncertainty in the appropriateness of assuming a constant rate. Scenario analysis has larger uncertainties.

Best supportive care and death health states and transition probabilities

Best supportive care (BSC): group of non-biologic supportive therapies

- On BSC, patients continue until end of the modelled time horizon or death
- PASI response levels are from placebo group data in base-case network meta-analysis

Death: patients can move to this state from any health state at any time

- Background age and sex* specific annual mortality rates from UK life tables, adjusted for increased risk of death in patients with moderate to severe psoriasis relative to matched controls (based on UK GPRD study; hazard ratio, 1.42; 95% CI: 1.25 to 1.62)
- Not affected by treatment or level of PASI response

*sex specific mortality rate combined into a blended rate using the proportion of men across the trials included in the network meta-analysis (68%)

Assumptions on treatment response

Assumptions (consistent with previous appraisals)	**Rationale**
Treatment waning: effect maintained with ongoing treatment	• limited long-term data on maintenance of PASI response • loss of response is main reason for long-term discontinuation (registry data) • non-responders included in annual drop out → others who continue assume to maintain response
Treatment efficacy: same regardless of previous use of therapies → placement of drug in sequence has no impact on drug's efficacy	• insufficient data from trials in network meta-analysis to do subgroup analysis for proposed population (previous use of systemic therapies/phototherapy) • efficacy of brodalumab was similar in subgroups with and without exposure to previous therapies (based on data at induction from AMAGINE pooled patient population)
3 scenario analyses: reduce efficacy for biologic-experienced patients in: 1) induction period only, 2) maintenance period only and 3) both induction and maintenance periods	

Treatment sequences

Sequence	1st	2nd	3rd	4th
1	**Brodalumab**	Ustekinumab	Secukinumab	BSC
2	Adalimumab	Ustekinumab	Secukinumab	BSC
3	Apremilast	Ustekinumab	Secukinumab	BSC
4	Dimethyl fumarate	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

- Sequences based on: British Association of Dermatologists guidelines, expert opinion (English advisory board of clinical and health economic experts)
- 2nd & 3rd therapies selected based on different mechanism of action than preceding line (consistent with ixekizumab NICE appraisal)
- Experts suggest likeliest 1st, 2nd & 3rd treatments: adalimumab, ustekinumab, secukinumab
- **Sensitivity analysis:** infliximab as alternative 3rd therapy

TNF-α inhibitor, IL-17 inhibitor, IL-12/IL-23 inhibitor, PDE-4 inhibitor, **Th1 and Th17 → Th2**

Treatment sequences – ERG comments

ERG's alternative base case using net monetary benefit framework gives identical results as company's base case

- Modelling treatment sequences vs comparison of single lines of therapy followed by best supportive care (BSC) more likely to reflect clinical practice and is consistent with previous appraisals
- Restrictive in number and position of brodalumab (only first line option in sequences)
- Modelling selective sequences could provide misleading cost-effectiveness estimates, especially if there are treatments in the sequences that are not cost effective
  - **ERG alternative approach:** net monetary benefit framework with rankings of each treatment compared with best supportive care
    - Treatment rankings from ERG's alternative base case are identical to company's base case → provides significant reassurance and confirmation on robustness of company's results

Serious adverse events modelled

- Treatments in model increases risk of serious infections (sepsis, tuberculosis, pneumonia, skin and soft tissue infection, bone and joint infection and urinary tract infection)
  - data on rates of infection based from:
    - Psoriasis Longitudinal Assessment and Registry registry study on 11,466 patients
    - trials from network meta-analysis (CLEAR, IXORA-S, AMAGINE-2 and -3)
- **Base case:** utility values (applied a multiplier for serious infection) and costs
- **3 scenario analyses:** non-melanoma skin cancer; other cancers; major adverse cardiac events

Utility values

Utility values based on AMAGINE-1 data for subgroup DLQI >10, adjusted for serious infections

- Utility values based on EQ-5D-3L data from AMAGINE-1 subgroup of DLQI >10
  - change in EQ-5D-3L score from baseline to week 12: stratified by level of PASI response
  - relationship between change in EQ-5D-3L score, PASI response and baseline DLQI explored using regression model
- degradation of utility due to serious infection included as multiplier (calculated using data from Diamantopoulos 2014 on utility for pneumonia, adjusted for expected duration of event, baseline age and gender of Sisk 1997 cohort)
- **Base case:** patients with PASI ≥12 and DLQ1 >10 (moderate to severe); regression model adjusted for baseline DLQI
- **4 scenario analyses** to address uncertainty of generalisability of AMAGINE-1 DLQI >10 data:
  - all patients in AMAGINE-1
  - 4th quartile of DLQI from TA103 (etanercept)
  - DLQI >10 estimates from TA350 (secukinumab)
  - median values from previous appraisals

DLQIDermatology Life Quality Index, PASIPsoriasis Area and Severity Index

Utility values – ERG comments

Brodalumab utility values lower at baseline with larger increments compared to previous appraisals

- Regression model should be adjusted for baseline EQ-5D (better goodness of fit), not baseline DLQI (3 sensitivity analyses showed consistent results when model was adjusted for baseline DLQI, baseline EQ-5D or baseline EQ-5D, PASI and DLQI)
- Consistent results in DLQI >10 subgroup and all patients: data from AMAGINE-1 generalisable to AMAGINE-2 and -3
- Uncertainty about generalisability of utility values to other trials in network meta-analysis: other appraisals have higher baseline utility and smaller increments

PASI response	Adjusted for baseline DLQI		Adjusted for baseline EQ-5D (ERG's base case)		e.g. TA350 (secukinumab)[a]
	DLQI>10 (base case)*	All patients^	DLQI>10	All patients	DLQI >10
Baseline	0.5206	0.6105	0.5206	0.6105	0.6402
PASI <50	(0.0158)	(0.0044)	(0.0035)	(-0.0037)	(0.109)
PASI 50–74	(0.1898)	(0.1349)	(0.2337)	(0.1574)	(0.193)
PASI 75–89	(0.2946)	(0.2441)	(0.3411)	(0.2631)	(0.226)
PASI 90–99	(0.3552)	(0.2798)	(0.3608)	(0.2895)	NR
PASI 100	(0.3680)	(0.2897)	(0.3774)	(0.2986)	NR

Increments in parentheses, *n=401, ^n=621, [a]Used EQ-5D-3L as in AMAGINE-1, n=3,286; [DLQI]Dermatology Life Quality Index, [PASI]Psoriasis Area and Severity Index; [NR]Not reported

Resource use and costs (1)

Drugs: patient access scheme discounts (**brodalumab 7 doses for induction**, apremilast, ixekizumab, secukinumab); biosimilar lowest cost (etanercept 50mg once weekly, infliximab includes wastage); list prices (adalimumab, dimethyl fumarate, ustekinumab 45mg)
ERG: 8 brodalumab doses for induction are more appropriate because information in the summary of product characteristics state that unit packs cannot be split (2 per pack)

Administration: only infliximab (intravenous infusion; mean of 1 consultant- and 1 non-consultant led non-admitted face-to-face follow-up appointment) £96.48
ERG: no administration costs for subcutaneous treatments are not consistent with other appraisals. Unlikely to generate significant resource use and cost implications for NHS

Monitoring visits (based on BAD guidelines)**:** 5 infliximab (£509.72 per year), 4 all other drugs (£407.78 per year)
ERG: fewer visits than in recent appraisals but valid justification given recent BAD guidelines. **ERG base case:** include additional 2 outpatient visits and associated blood tests costs for dimethyl fumarate

Resource use and costs (2)

Best supportive care (based on Fonia 2010 as previous appraisals): £5,283.11 per year (£203.20 per 2 week cycle)
ERG: costs are correctly estimated and consistent with source and previous appraisals

Non-responder (excluded in base case): patients whose psoriasis does not respond to biologics and switch to best supportive care may incur additional healthcare costs, but these costs are already included in the inpatient costs in best supportive care (from Fonia).
Scenario analysis: non-responder costs for 10.3 inpatient days (£449 per day)

ERG base case: include non-responder costs of £128 per 2 week cycle, based on TA475 (dimethyl fumarate) and TA442 (ixekizumab)

Adverse events (average cost of 6 serious infections)**:** £2,653
ERG: assumptions and estimates are appropriate

ERG base case

- Model: net monetary benefit analysis of single treatments vs best supportive care
  - address misleading cost-effectiveness estimates from restricted treatment sequences that may include treatments that are not cost effective
- Clinical effectiveness input: derived from placebo-adjusted network meta-analysis
  - improved goodness of fit
- Utility values: used regression model adjusted for baseline EQ-5D only for DLQI >10 subgroup
  - improved goodness of fit
- Brodalumab dosing assumptions from 7 to 8 doses
  - more appropriate given the inability to split packs
- Inclusion of non-responder costs
  - consistent with recent appraisals

Results in Part 2 only

- Confidential PAS for apremilast, brodalumab, ixekizumab and secukinumab
- Results for company's base case, scenario and sensitivity analyses are largely consistent
- Committee will see:
  - Company's base case deterministic and probabilistic results
  - ERG's base case probabilistic results

Innovation

- Company suggests the following may not be included in the incremental cost-effectiveness ratio. Brodalumab:
  - has the potential to deliver complete skin clearance for many patients
  - is efficacious in the treatment of nail and scalp psoriasis
  - is associated with rapid responses while requiring fewer induction doses than the anti-TNF therapies
  - delivers sustained responses, even after treatment interruption
  - provides clinicians and patients with an alternative choice within the interleukin-17 class of biological therapies

Equality considerations

- As in previous appraisals, the following issues have been identified by:
  - Psoriasis Area and Severity Index (PASI) may underestimate disease severity in people with darker skin as redness may be less evident (key component of PASI)
  - Dermatology Life Quality Index (DLQI) underestimates the impact of people who are not sexually active or older or socially isolated and does not capture anxiety and depression

Authors

- **Sharlene Ting**
  Technical Lead
- **Ahmed Elsada**
  Technical Adviser
- with input from the Lead Team (**Mark Chapman, Dani Preedy, Steve Smith**)

Additional slides (non-essential reading)

Analysis sets and handling missing data

Safety analysis set	All randomised patients who received at least 1 treatment dose
End of induction period (week 12)	**Full analysis set:** all patients randomised to treatment regardless of actual treatment received **Missing data** • Non-responder imputation (dichotomous endpoints) • Multiple imputation for Nail Psoriasis Severity Index (AMAGINE-2 and -3)
At end of maintenance (week 52)	• AMAGINE-1: all patients who responded to sPGA (0 or 1) and were re-randomised to brodalumab • AMAGINE-2 and -3 (**Efficacy analysis set**): all brodalumab patients re-randomised at week 12 **Missing data** • As observed with no imputation: patients re-randomised to placebo receiving rescue therapy (AMAGINE-1); patients on placebo or ustekinumab during induction who received brodalumab at weeks 12 or 16 (AMAGINE-2 and -3) • All other patients: non-responder* imputation (dichotomous endpoints) or last observation carried forward (continuous outcomes)
Open-label extension	All patients who entered open-label extension phase at week 52 (as observed with no imputation)

*Non-responder defined as single sPGA ≥3 or persistent sPGA 2 over at least 4 weeks. Data from patients who were on ustekinumab but received rescue therapy or switched treatment in AMAGINE-2 and -3 were considered missing. sPGAStatic Physician Global Assessment

AMAGINE-1 participant flow

Treatment discontinuation because of adverse events were low and similar for brodalumab and placebo groups at 12 weeks

	Brodalumab 210mg Q2W			Placebo
Randomised			222	220
Discontinued treatment			10 (2 AE)	12 (3 AE)
Completed induction (12 weeks)			212	209
	Re-randomised or switching based on sPGA response			**Switched to brodalumab 210mg Q2W**
	Re-randomised to brodalumab 210mg Q2W	**Re-randomised to placebo**	**Switched to brodalumab 210mg Q2W**	
	83	**84**	**45**	**208**
Discontinued treatment	4 (2 AE)	3 (0 AE)	14 (2 AE)	20 (4 AE)
Re-treated with brodalumab	*5*	*79*	*NR*	*NR*
Completed maintenance (52 weeks)	74	2	31	187

AE Adverse event, Q2W Every 2 weeks, sPGA Static Physician Global Assessment (sPGA 0 or 1 → re-randomised; sPGA ≥2 → switch)

AMAGINE-2 and -3 participant flow

Treatment discontinuation was generally higher with brodalumab compared to ustekinumab

	AMAGINE-2			AMAGINE-3		
	BROD	UST	Placebo	BROD	UST	Placebo
Randomised	612	300	309	624	313	315
Received treatment (SAS)	612	300	309	622	313	313
Discontinued treatment	15 (3 AE)	9 (2 AE)	9	16 (4 AE)	10 (1 AE)	14
Completed induction (12 weeks)	597	291	300	608	303	301
Entered maintenance phase (EAS)	334*	289	297^	342*	301	298^
Received treatment (SAS)	334	288	297	341	301	297
Discontinued treatment[b]	14	7	22	13	7	22
Rescue therapy	101	133	0	100	140	0
Completed maintenance (52 weeks)	219	148	274	229	152	275
Open-label extension[a]	1601			1656		

[AE]Adverse events, [BROD]Brodalumab 210mg every 2 weeks, [EAS]Efficacy analysis set, [SAS]Safety analysis set, [UST]Ustekinumab, *Re-randomised to brodalumab 210mg every 2 weeks, ^Switched to brodalumab 210mg every 2 weeks, [a]Includes other re-randomised brodalumab groups at lower dose (140mg every 2, 4 and 8 weeks). [b]Different results reported in Tables 122 (AMAGINE-2) and 123 (AMAGINE-3; Appendix L). Note: Discontinuation because of adverse events likely to be underestimated because similar reasons were included in "Other" category (Company clarification response: A11)

Adverse events (safety analysis set) during **induction**

ERG: brodalumab had higher proportion of any adverse events in AMAGINE-1 than placebo

Induction phase (12 weeks)	% Adverse events			
	Any[b]	Serious	Death	Leading to discontinuation from study or drug
AMAGINE-1				
Brodalumab (n=222)[a]	59	1.8	0	1.8
Placebo (n=220)	51	1.4	0	2.4
AMAGINE-2				
Brodalumab (n=612)[a,c]	58	1	0.2	2
Ustekinumab (n=300)	59	1.3	0	2
Placebo (n=309)	53	2.6	0	0.3
AMAGINE-3				
Brodalumab[a] (n=622)	57	14	0	1.9
Ustekinumab (n=313)	54	0.6	0	0.9
Placebo (n=313)	49	1	0	1.6

[a]Brodalumab 210mg every 2 weeks, [b]Most common adverse events for all groups in AMAGINE-2 and -3 were injection site reactions; mild or moderate *Candida* infections and neutropaenia occurred more frequently in brodalumab than other groups, [c]1 suicide attempt, [n]Number of patients

Brodalumab phase 2 trials

ERG: agrees submission should focus on larger AMAGINE trials

- Company did not include 2 smaller phase 2 studies (brodalumab vs placebo) in submission because of space constraints but included them in the network meta-analysis

➢ Papp et al (2012): n=40 brodalumab 210mg every 2 weeks, n=38 placebo

➢ Nakagawa et al (2016; Japanese study): n=37 brodalumab 210mg every 2 weeks, n=38 placebo.

  – Brodalumab significantly more effective than placebo at 12 weeks in PASI 75, PASI 90, PASI 100 and sPGA 0 or 1, with similar response rates in PASI 90 and sPGA as those in AMAGINE

[PASI]Psoriasis Area and Severity Index, [sPGA]Static Physician Global Assessment (0=clear, 1=almost clear), [n]Number of patients

Serious infection modelled

Treatment	Serious infection rate (p/100 patient-years)	Source
Best supportive care	1.05 (0.75–1.43)	Kalb 2015 (non-methotrexate/non-biologic population value)
Adalimumab	1.97 (1.61–2.39)	Kalb 2015
Etanercept	1.47 (1.10–1.91)	Kalb 2015
Infliximab	2.49 (1.88–3.23)	Kalb 2015
Ustekinumab	0.83 (0.61–1.09)	Kalb 2015
Brodalumab	1.19	Brodalumab vs ustekinumab rate ratio (1.43, 95% CI 0.5 to 4.08) meta-analysed from week 52 AMAGINE-2 & -3 serious infections rate
Secukinumab	0.83 (0.61–1.09)	Assumed same as ustekinumab based 52 weeks in CLEAR study (secukinumab vs ustekinumab)
Ixekizumab	0.83 (0.61–1.09)	Assumed same as ustekinumab based on 24 weeks in IXORA-S (ixekizumab vs ustekinumab)
Apremilast	1.28 (0.73–2.09)	Kalb 2015 (non-methotrexate/non-biologic population value)
Dimethyl fumarate	1.28 (0.73–2.09)	Kalb 2015 (non-methotrexate/non-biologic population value)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Brodalumab for treating moderate to severe plaque psoriasis in adults [ID878]

Document A

Company evidence submission summary for committee

LEO Pharma confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

September 2017

File name	Version	Contains confidential information	Date
Brodalumab STA [ID878] Section A [redacted].docx	**1.1**	**No**	**12 October 2017**

Instructions for companies

This is the template you should use to summarise your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision-making.

This submission summary must not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted. Please submit a draft summary with your main evidence submission. The NICE technical team may request changes later.

When cross referring to evidence in the main submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Summary length excluding template and references: 25 pages.

Tables and figures

Submission summary

A.1 Health condition

Psoriasis is a chronic, inflammatory, immune-mediated skin disorder which follows a relapsing–remitting pattern (1). Psoriasis affects men and women equally, is more common among Caucasians than other ethnic groups, and can occur at any age; onset in the majority of cases occurs before 35 years of age (1, 2). In the UK, psoriasis affects 3% of the population (3), of whom approximately 20% (corresponding to ~230,000 people in England) have moderate-to-severe disease (4).

Common symptoms of chronic plaque psoriasis include scaling, itching, redness, tightness of the skin, bleeding and burning, which can affect sleep and physical functioning, and restrict activities of daily living and work productivity (5-9). Chronic plaque psoriasis is associated with comorbidities including other autoimmune diseases, hyperlipidaemia, hypertension and diabetes (10, 11), and is a risk factor for major adverse cardiac events (12) and death (13).

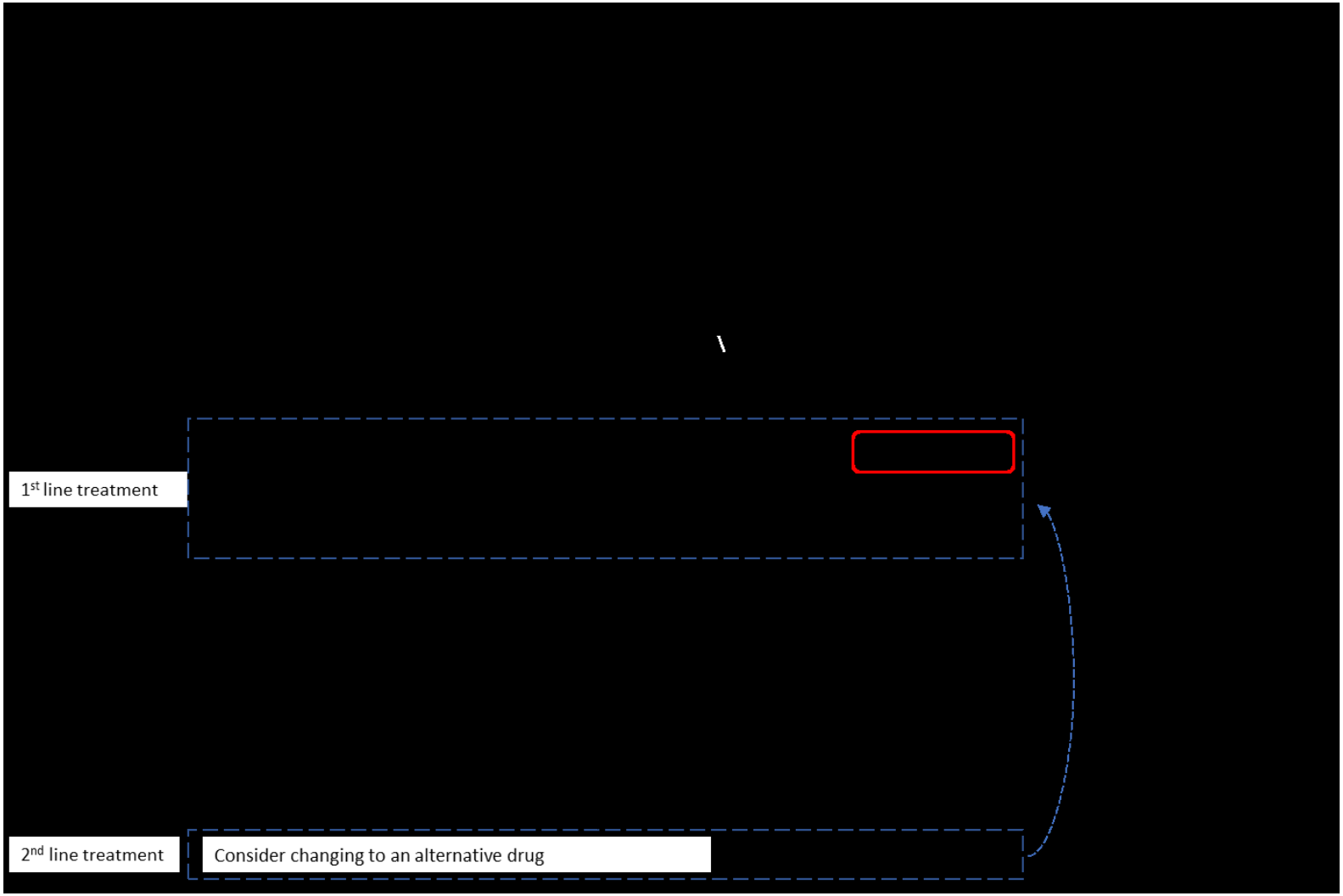
Chronic plaque psoriasis has a significant impact on patients' health-related quality of life (HRQoL). Many patients suffer from isolation, stigmatisation, embarrassment, and difficulties in sexual relations (14-16), and psoriasis can lead to reduced levels of employment and income, and an increased risk of depression and anxiety (1, 11, 17).

The IL-17 pathway plays a central role in psoriasis pathogenesis and blocking the effects of the pro-inflammatory cytokine IL-17 on keratinocytes is a critical therapeutic goal (18). Brodalumab is the first psoriasis therapy to act on the IL-17 receptor on keratinocytes and immune cells, and blocks the biological activity of multiple IL-17 isoforms, inhibiting the inflammation and clinical symptoms of psoriasis (18).

A.2 Clinical pathway of care

Brodalumab should be considered as a treatment option for moderate-to-severe psoriasis, alongside the biological therapies adalimumab, etanercept, ixekizumab, secukinumab and ustekinumab, in patients whose psoriasis has not responded to standard systemic therapies or who are intolerant of, or have a contraindication to, these treatments (Figure 1).

Figure 1 Proposed position of brodalumab within the treatment pathway for patients with moderate-to-severe psoriasis, in accordance with NICE recommendations – B.1.3.5, page 19.



DLQI, Dermatology Life Quality Index; DMF, dimethyl fumarate; IL, interleukin; IL-17 RA, IL-17-receptor A; PASI, Psoriasis Area Severity Index; TNF, tumour necrosis factor.

A.4 The technology

Table 1 Technology being appraised – B.1.2 (page14)

UK approved name and brand name	Brodalumab (Kyntheum®)
Mechanism of action	Brodalumab is the first fully human immunoglobulin G2b monoclonal antibody with a high affinity for IL-17 receptor A
Marketing authorisation/CE mark status	Brodalumab (Kyntheum®) was granted a European marketing authorisation (EU/1/16/1155/001) on 17 July 2017
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Brodalumab (Kyntheum®) is indicated for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy
Method of administration and dosage	The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks
Additional tests or investigations	Brodalumab has a similar administration profile to other biological treatments available to NHS England patients; no additional tests or investigations are required
List price and average cost of a course of treatment	NHS list price: £1280 per pack of 2 syringes Annual cost of treatment (list price): year 1, £17,280; subsequent years, £16,640
Patient access scheme (if applicable)	A confidential patient access scheme (PAS) has been agreed and approved by the Patient Access Scheme Liaison Unit (PASLU)/Department of Health. [redacted]

A.5 Decision problem and NICE reference case

The submission covers the technology's full marketing authorisation for this indication.

The company submission is consistent with the final NICE scope and the NICE reference case.

Table 2 The decision problem – B.1.1 (page13)

	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	Moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy, and for whom standard systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated	As per summary of product characteristics (SmPC) and anticipated placement in the treatment pathway
Intervention	Brodalumab	Brodalumab 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks	As per reference case and final label
Comparator(s)	If non-biologic systemic treatment or phototherapy is suitable: • Systemic non-biological therapies (including acitretin, ciclosporin, dimethyl fumarate (subject to ongoing NICE appraisal), fumaric acid esters, methotrexate)	For people with severe or very severe psoriasis for whom standard systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated: • TNF-alpha inhibitors (etanercept, infliximab, adalimumab)	In clinical practice, brodalumab is likely to be offered at a similar place in the clinical pathway as existing NICE approved biological treatments, apremilast and dimethyl fumarate, i.e. after standard systemic therapies have failed, are contraindicated or are not tolerated. This is in line with the NICE pathway for the use of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Phototherapy with ultraviolet (UVB) radiation For people with severe or very severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated: • TNF-alpha inhibitors (etanercept, infliximab, adalimumab) • Ustekinumab • Secukinumab • Apremilast • Ixekizumab • Dimethyl fumarate (subject to ongoing NICE appraisal) • Best supportive care	• Ustekinumab • Secukinumab • Apremilast • Ixekizumab • Dimethyl fumarate • Best supportive care	biologics in psoriasis (1). Based on this likely placement in the treatment pathway, the most appropriate comparators for brodalumab are other biologic treatments, apremilast and dimethyl fumarate, not standard systemic therapies (e.g. acitretin, ciclosporin, fumaric acid esters, methotrexate) or phototherapy.
Outcomes	• Severity of psoriasis (including the Psoriasis Area Severity Index [PASI]) • Psoriasis symptoms on the face, scalp and nails • Mortality • Response rate • Relapse rate • Adverse effects of treatment • Health-related quality of life (including dermatology quality of life index [DLQI]).	• Severity of psoriasis (including the Psoriasis Area Severity Index [PASI]) • Psoriasis symptoms on the face, scalp and nails • Mortality • Response rate • Relapse rate • Adverse effects of treatment • Health-related quality of life (including dermatology quality of life index [DLQI]).	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • previous use of systemic non-biological therapy • previous use of biological therapy • severity of psoriasis (moderate, severe)	The following subgroups were analysed: • severity of psoriasis (moderate, severe, by PASI score) • severity of psoriasis (by DLQI score) • previous use of systemic non-biological therapy or phototherapy • previous use of systemic non-biological therapy • number of previous systemic therapies • systemic agent failure or contraindication • previous use of biological therapy • previous failure of biological therapy • previous use of anti-TNF therapy	All subgroups in scope were assessed; additional subgroups of potential relevance were also included

A.6 Clinical effectiveness evidence

Brodalumab has been investigated for the treatment of moderate-to-severe plaque psoriasis in three phase 3 randomised controlled trials (RCTs): AMAGINE-1 (NCT01708590), AMAGINE-2 (NCT01708603) and AMAGINE-3 (NCT01708629) (Table 3). The identical AMAGINE-2 and AMAGINE-3 trials compared the efficacy and safety of brodalumab with ustekinumab and placebo – these trials form the main source of evidence in this submission. Supporting evidence of the effect of brodalumab is taken from AMAGINE-1, a multicentre, international, phase 3 placebo-controlled trial (19). All three AMAGINE trials were included in the network meta-analysis (NMA) that was used in the economic model (see sections A.8 and main evidence submission, B.3).

Table 3 Clinical effectiveness evidence

Study title	**AMAGINE-2 and AMAGINE-3 (2015) (20)**	**AMAGINE-1 (2016) (19)**
Study design	RCTs: multicentre, randomised, controlled, parallel-group, placebo- and active-controlled phase 3 trials with 12-week induction phase and 40-week maintenance phase	RCTs: multicentre, randomised, controlled, parallel-group, placebo-controlled phase 3 trials with 12-week induction phase and 40-week maintenance / withdrawal phase
Population	Adults aged 18 to 75 years who were candidates for biological therapy for stable moderate-to-severe plaque psoriasis of at least 6 months' duration and who had a PASI score of 12 or higher, an sPGA score of 3 or higher, and involvement of 10% or more of the body surface area	
Intervention(s)	Brodalumab 210 mg Q2W or brodalumab 140 mg Q2W [a]	
Comparator(s)	Placebo or ustekinumab	Placebo
Outcomes specified in the decision problem	**PASI 100, PASI 90 and PASI 75 response rates** Improvement in DLQI score Improvement in NAPSI score (nail involvement)	**PASI 100, PASI 90 and PASI 75 response rates** Improvement in DLQI score Improvement in PSSI score (scalp involvement) **EQ-5D utility values**
Reference to section in submission	B.2.2 (page 23), B.2.3 (page 26), B.2.6.2 (page 43), B.2.10.1 (page 79)	B.2.2 (page 23), B.2.3 (page 26), B.2.6.3 (page 57), B.2.10.2 (page 84)

[a] Brodalumab 140 mg Q2W is outside the label for brodalumab in the treatment of moderate-to-severe plaque psoriasis; these results are not described in detail in this submission, but are summarised in Appendix L and published in Lebwohl *et al.* 2015 (20) and Papp *et al.* 2016 (19).
Sources: Lebwohl *et al.* 2015 (20), Papp *et al.* 2016 (19).
DLQI, Dermatology Life Quality Index; EQ-5D, EuroQol-5D questionnaire; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; PSSI, Psoriasis Scalp Severity Index; Q2W, every 2 weeks.

The primary endpoint in AMAGINE-2 and AMAGINE-3 was the proportion of patients treated with brodalumab 210 mg Q2W who had a 100% improvement in Psoriasis Area and Severity Index (PASI) score (PASI 100) at week 12, compared with ustekinumab. In AMAGINE-1, the week 12 co-primary endpoints were the proportion of patients with a 75% improvement in PASI score (PASI 75), and the proportion achieving a static Physician's Global Assessment (sPGA) response (clear [0] or almost clear [1]) (19, 20).

Two additional phase 2 studies of brodalumab were included in the NMA (21, 22). Because data are available from the three phase 3 AMAGINE trials, the phase 2 studies are not described in detail in this submission.

Patients in the AMAGINE studies were eligible to enter an open-label extension phase, which provides additional evidence for the long-term efficacy and safety of brodalumab 210 mg Q2W (see main evidence submission, B.2.6.4, page 64). This study was not included in the economic model because of its open-label, uncontrolled design.

A.7 Key results of the clinical effectiveness evidence

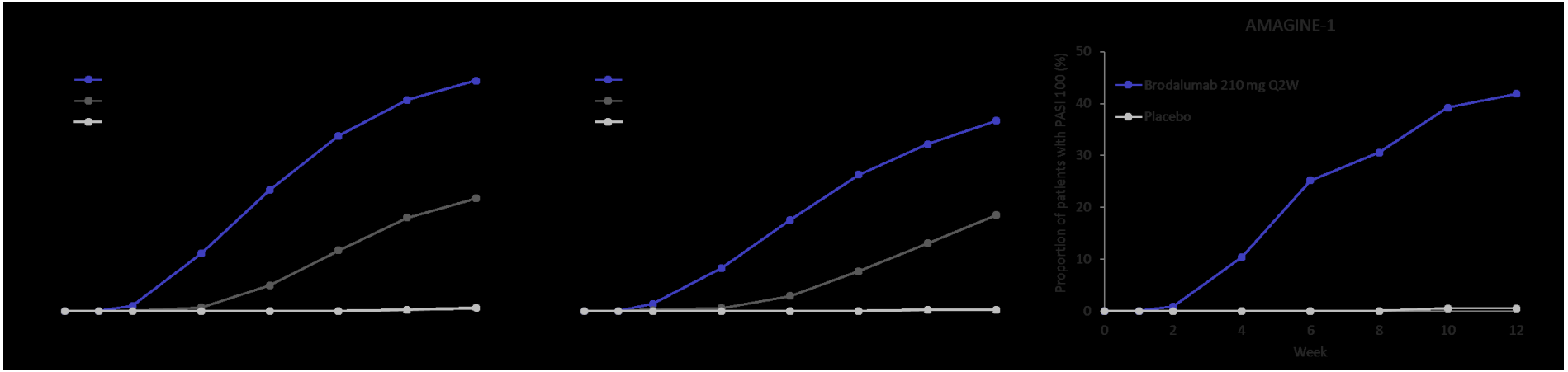
A.7.1 PASI 100 responses at 12 weeks – B.2.6.2.2 (page 45) and B.2.6.3.2 (page 58)

Almost twice as many patients achieved PASI 100 with brodalumab than with ustekinumab: in AMAGINE-2, 44.4% (95% CI, 40.5–48.5%) of patients in the brodalumab 210 mg Q2W group (n = 612) had a PASI 100 response at week 12, compared with 21.7% (17.1–26.8%) of those in the ustekinumab group (n = 300; $p < 0.001$). Similarly, in AMAGINE-3, PASI 100 was achieved by 36.7% (32.9–40.6%) of patients receiving brodalumab 210 mg Q2W (n = 624) and 18.5% (14.4–23.3%) of those receiving ustekinumab (n = 315; $p < 0.001$; B.2.6.2.2, page 45) (20).

The response to brodalumab 210 mg Q2W was more rapid than that to ustekinumab (Figure 2), with a significant difference seen as early as week 4: [redacted] receiving brodalumab 210 mg Q2W in AMAGINE-2 and [redacted] in AMAGINE-3 achieved PASI 100 at week 4, compared with [redacted] and [redacted] in the respective ustekinumab groups (both [redacted]) (23, 24).

PASI 100 response rates with brodalumab 210 mg Q2W in AMAGINE-1 (n = 222) were consistent with the results of the AMAGINE-2 and AMAGINE-3 studies (Figure 2; B.2.6.3.2, page 59) (19).

Figure 2 PASI 100 responses at week 12 (FAS, NRI; B.2.6.2.2, Figure 6, page 46 and B.2.6.3.2, Figure 20, page 59)



Missing data were imputed as nonresponses (see main evidence submission, section B.2.4.4).
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index.
Source: Lebwohl *et al*. 2015 (25).

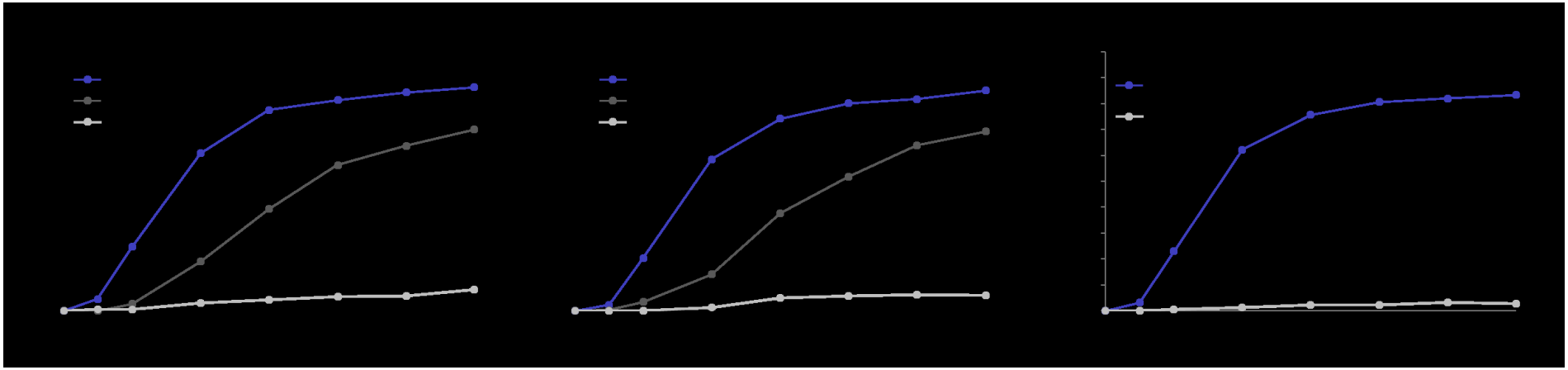
A.7.2 PASI 75 responses at 12 weeks – B.2.6.2.2 (page 47) and B.2.6.3.2 (page 58)

Significantly more patients achieved PASI 75 with brodalumab than with ustekinumab: in AMAGINE-2, 86.3% (95% CI, 83.3–88.9%) of patients in the brodalumab 210 mg Q2W group had a PASI 75 response at week 12, compared with 70.0% (64.5–75.1%) of those in the ustekinumab group ($p < 0.001$). Similarly, in AMAGINE-3, PASI 75 was achieved by 85.1% (82.1–87.8%) of patients treated with brodalumab 210 mg Q2W and 69.3% (63.9−74.4%) of those receiving ustekinumab ($p < 0.001$; B.2.6.2.2, page 47) (20).

The response to brodalumab 210 mg Q2W was more rapid than that to ustekinumab (Figure 3), with a significant difference seen as early as week 1: [redacted] receiving brodalumab 210 mg Q2W in AMAGINE-2 and [redacted] in AMAGINE-3 achieved PASI 75 at week 1, compared with [redacted] and [redacted] in the respective ustekinumab groups (23, 24).

Responses in AMAGINE-1 were similar to those in AMAGINE-2 and AMAGINE-3, with 83% of patients receiving brodalumab 210 mg Q2W having a PASI 75 response at week 12, compared with 3% of the placebo group (n = 220; $p < 0.001$; Figure 3; B.2.6.3.2, page 58) (19).

Figure 3 PASI 75 responses at week 12 (FAS, NRI; B.2.6.2.2, Figure 8, page 47 and B.2.6.3.2, Figure 19, page 58)



Missing data were imputed as nonresponses (see main evidence submission, section B.2.4.4).
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index.
Source: Lebwohl *et al*. 2015 (25).

A.7.3 Maintenance of responses to 52 weeks – B.2.6.2.3 (page 51) and B.2.6.3.4 (page 61)

Among patients receiving constant brodalumab 210 mg Q2W in AMAGINE-2 (n = 189) and AMAGINE-3 (n = 194), PASI 75 and PASI 90 response rates at week 12 were maintained to week 52, while PASI 100 response rates increased slightly during the maintenance phase (B.2.6.2.3, Figure 14, page 53) (20). [redacted]

Among patients who switched to brodalumab 210 mg Q2W at week 16 after inadequate response to ustekinumab, 91% in AMAGINE-2 [n = 55] and 82% in AMAGINE-3 [n = 69] had PASI 75 responses at week 52, with 46% and 40%, respectively, achieving PASI 100 (B.2.6.2.3, Table 18, page 54) (20).

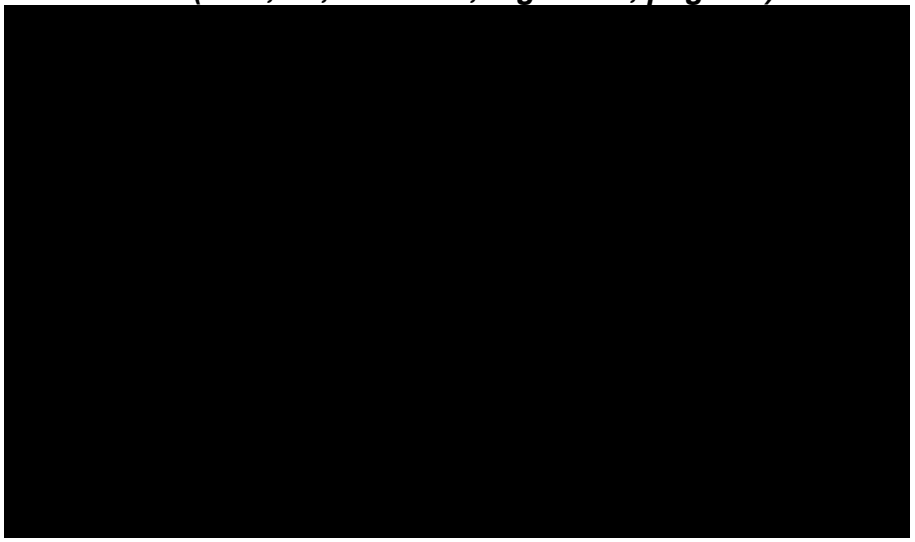
The design of AMAGINE-1 allowed the efficacy of brodalumab re-treatment after loss of treatment response to be tested. In AMAGINE-1, 84 patients with an initial sPGA response on brodalumab 210 mg Q2W were re-randomised to placebo at week 12, and 79 experienced a return of disease. Of these patients, 97% recaptured sPGA response after 12 weeks of re-treatment with brodalumab 210 mg Q2W, and 84% achieved an sPGA score of 0 (clear) (B.2.6.3.4, page 61).

A.7.4 Improvements in nail and scalp symptoms at 12 weeks – B.2.6.2.2 (page 50) and B.2.6.3.2 (page 59)

In AMAGINE-2 and AMAGINE-3, nail involvement was assessed at baseline and week 12 with the Nail Psoriasis Severity Index (NAPSI) (25). Patients receiving brodalumab 210 mg Q2W in AMAGINE-2 and AMAGINE-3 had reductions in NAPSI score at week 12: [redacted]

In AMAGINE-1, scalp involvement was assessed at baseline and week 12 with the Psoriasis Scalp Severity Index (PSSI). At baseline, [redacted] patients randomised to placebo and [redacted] randomised to brodalumab 210 mg Q2W in AMAGINE-1 had PSSI scores of ≥ 15. [redacted]

Figure 4 Mean NAPSI score at baseline and week 12 in AMAGINE-2 (FAS, MI; B.2.6.2.2, Figure 12, page 50)



Analysis includes only patients with baseline NAPSI score of ≥ 6. Multiple imputation was used to impute missing data. † $p < 0.001$ vs placebo. No p value for brodalumab 210 mg Q2W vs ustekinumab was calculated.
FAS, full analysis set; MI, multiple imputation; NAPSI, Nail Psoriasis Severity Index. Source: AMAGINE-2 CSR (23).

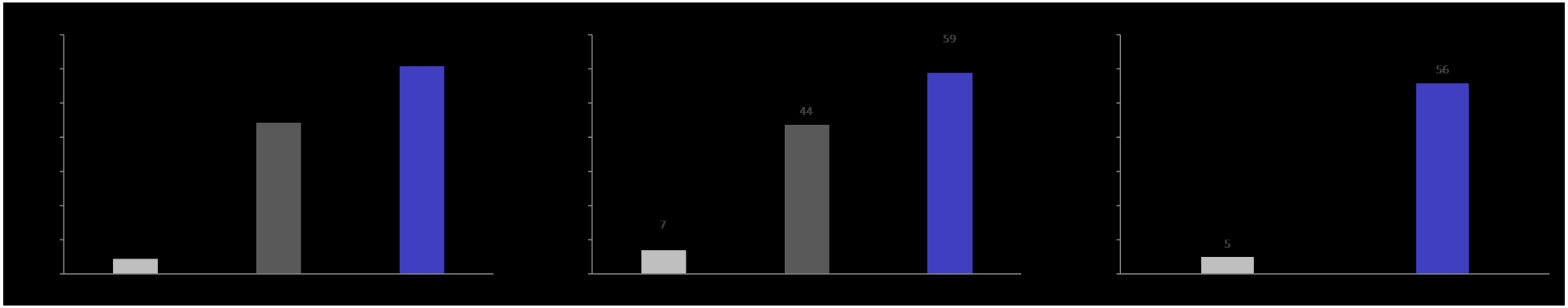
Figure 5 PSSI 75 responses at week 12 in AMAGINE-1 (FAS, NRI; B.2.6.3.3, Figure 21, page 60)

Missing data were imputed as nonresponses (see section B.2.4.4).
FAS, full analysis set; NRI, non-responder imputation; PSSI, Psoriasis Scalp Severity Index. † $p < 0.001$ vs placebo. Bars indicate 95% confidence intervals.
Q2W, every 2 weeks. Source: AMAGINE-1 CSR (26).

A.7.5 HRQoL improvements at 12 weeks – B.2.6.2.4 (page 55) and B.2.6.3.5 (page 61)

Treatment with brodalumab 210 mg Q2W was associated with an increased likelihood versus ustekinumab of psoriasis no longer having an effect on a patient's life, as assessed with the Dermatology Life Quality Index (DLQI). At week 12 in AMAGINE-2 and AMAGINE-3, 61% and 59%, respectively, of patients in the brodalumab 210 mg Q2W groups had DLQI scores of 0 or 1 at week 12, compared with 44% in both ustekinumab groups (Figure 6) (20); in AMAGINE-1, 56% of patients in the brodalumab 210 mg Q2W groups had DLQI scores of 0 or 1 (B.2.6.3.5, page 61) (19).

Figure 6 Proportion of patients with DLQI 0 or 1 at week 12 (FAS, NRI)



Missing values were imputed as nonresponses (see main evidence submission, section B.2.4.4).
DLQI, Dermatology Life Quality Index; FAS, full analysis set; NRI, non-responder imputation; Q2W, twice weekly.
Sources: AMAGINE-2 CSR (23); AMAGINE-3 CSR (24); Strober *et al.* 2016 (27).

AMAGINE-1 included the Hospital Anxiety and Depression Scale (HADS) and the EuroQol-5D questionnaire (EQ-5D). From baseline to 12 weeks, patients had significantly larger reductions in HADS depression and anxiety scores with brodalumab 210 mg Q2W than with placebo. Among patients with moderate or severe depression and anxiety, HADS scores improved with brodalumab (B.2.6.3.5, page 63) (19).

Baseline EQ-5D scores in the AMAGINE-1 placebo and brodalumab 210 mg Q2W groups were 0.62 and 0.60, respectively. At 12 weeks, the mean EQ-5D score was significantly higher in the brodalumab group than in the placebo group (0.85 vs 0.61; $p < 0.001$; B.2.6.3.5, page 63) (28).

A.7.6 Summary of safety evidence – B.2.10 (page 79)

The overall safety profile of brodalumab 210 mg Q2W in the AMAGINE-2 and AMAGINE-3 phase 3 RCTs was comparable to that of ustekinumab. In all three AMAGINE trials, the frequency of serious adverse events and events leading to discontinuation was low, and was similar across randomised groups in both induction and maintenance phases. Overall, the most common adverse event during the induction phase of the AMAGINE trials was nasopharyngitis. The most common adverse events of interest over 52 weeks were injection site reactions and *Candida* infections; all infections were graded as mild or moderate, and none was systemic.

A.7.7 Suicidal ideation and behaviour – B.2.10.5 (page 88)

A small proportion of patients in the AMAGINE trials experienced suicidal ideation, and in total there were four completed suicides; however, no causal relationship has been established between brodalumab and suicidal ideation and behaviour (B.2.10.5, page 88). An analysis conducted by the FDA Division of Epidemiology found similar levels of suicidal ideation and behaviour events with brodalumab, apremilast, ixekizumab, and infliximab; the overall rate of suicidal behaviour (attempted and completed) for brodalumab was the same as that for ixekizumab (0.14 events per 100 patient-years), even though patients with a history of suicidal behaviour were excluded from the trials of ixekizumab but not brodalumab (B.2.10.5, page 89) (29). Overall, the data suggest that the risk of suicidal ideation and behaviour with brodalumab is no higher than that seen with other biological therapies.

A.8 Evidence synthesis

The base-case NMA of PASI response outcomes included data from 59 RCTs involving 28,346 patients (B.2.9, page 66). All of the scope comparators were included in the network, as were standard systemic therapies and unlicensed doses of relevant comparators where this contributed additional indirect evidence for licensed doses. [redacted]

The PASI responses predicted in the NMA for brodalumab 210 mg Q2W, ustekinumab and placebo were similar to those reported in the AMAGINE trials, suggesting that the direct and indirect evidence in the NMA are generally consistent. In addition, the results of the base-case analyses were robust to changes in the inclusion/exclusion criteria for the networks, including exclusion of evidence for unlicensed therapies and unapproved doses of relevant comparators, did not change the ranking of therapies in the base case (B.2.9.3.2, page 75).

The results of the NMA were used as the source of clinical efficacy data in the economic model (section B.3, page 102).

Table 5 Treatment effects at each level of PASI response – base-case NMA (B2.9.2, Tables 27 and 28, pages 73 and 74).

Risk ratio versus placebo, median (95% Credible Interval)				
Treatment	**PASI 50**	**PASI 75**	**PASI 90**	**PASI 100**
Brodalumab 210mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg Q2W	5.61 (4.91 to 6.44)	11.45 (9.69 to 13.61)	31.82 (25.61 to 39.69)	121.9 (91.06 to 163)
Apremilast 30mg BID	3.19 (2.74 to 3.69)	4.74 (3.85 to 5.78)	8.16 (6.1 to 10.72)	16.24 (10.93 to 23.57)
Dimethyl Fumarate	2.49 (1.73 to 3.39)	3.35 (2.04 to 5.16)	5.01 (2.55 to 9.14)	8.31 (3.37 to 18.97)
Etanercept 50 mg / week	4.06 (3.57 to 4.66)	6.79 (5.69 to 8.15)	13.81 (10.8 to 17.71)	34.27 (24.45 to 48.19)
Infliximab 5mg/kg	6.18 (5.36 to 7.16)	13.74 (11.48 to 16.58)	44.42 (35.13 to 56.51)	213.8 (155.7 to 295.2)
Ixekizumab 80mg Q2W	6.57 (5.66 to 7.67)	15.71 (13.02 to 19.08)	58.75 (46.63 to 74.63)	361.9 (272.2 to 486.3)
Secukinumab 300mg	6.34 (5.49 to 7.38)	14.53 (12.14 to 17.52)	49.61 (39.68 to 62.6)	261 (196.4 to 350.3)
Ustekinumab 45mg	5.87 (5.12 to 6.76)	12.43 (10.49 to 14.84)	36.79 (29.63 to 45.99)	154.8 (116.4 to 206.5)
Ustekinumab 90mg	6.02 (5.24 to 6.97)	13.08 (10.99 to 15.69)	40.42 (32.34 to 50.89)	181.5 (135.1 to 245.2)
Ustekinumab (in-label dose)	5.84 (5.1 to 6.72)	12.32 (10.4 to 14.71)	36.22 (29.13 to 45.4)	150.7 (112.9 to 202.6)
Risk ratio for brodalumab 210 mg Q2W versus comparator, median (95% CrI)				
Treatment	**PASI 50**	**PASI 75**	**PASI 90**	**PASI 100**
Adalimumab 40mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast 30mg BID	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl Fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50 mg / week	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300mg	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 45mg	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90mg	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab (in-label dose)	[redacted]	[redacted]	[redacted]	[redacted]

Risk ratios in bold indicate statistically significant differences. Results are only presented for licensed doses of therapies in the technology appraisal scope, even though unlicensed doses and standard systemic therapies were included in the evidence network. [a] 95% credible interval does not span 1.
BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

A.9 Key clinical issues

- A limitation of the AMAGINE-2 and AMAGINE-3 studies is that patients randomised to ustekinumab were switched to brodalumab rescue therapy if they had an inadequate response at week 16. This approach reduced the amount of data on ustekinumab, but allowed evaluation of the efficacy of brodalumab treatment following inadequate response to ustekinumab (see section B.2.6.2.3, page 54).
- As for other clinical trials in psoriasis, a limitation of the AMAGINE studies is the lack of direct comparisons with active comparators other than ustekinumab. This limitation has been addressed by conducting an NMA.

A.10 Overview of the economic analysis

A schematic diagram illustrating the structure of the model is shown in Figure 7. The model consists of four treatment-related health states defined as induction, maintenance, best supportive care (BSC) and death. In addition, patients can have one of five categories of PASI response: PASI 0–49, PASI 50–74, PASI 75–89, PASI 90–99 or PASI 100.

The treatment sequences included in the model comprise three lines of active therapy, followed by BSC. The first position of each treatment sequence is occupied by one of the comparators of brodalumab in line with the technology appraisal scope. Where possible, second- and third-line therapies were selected that had a different mechanism of action to the preceding line; this approach is consistent with the recent ixekizumab technology appraisal (30).

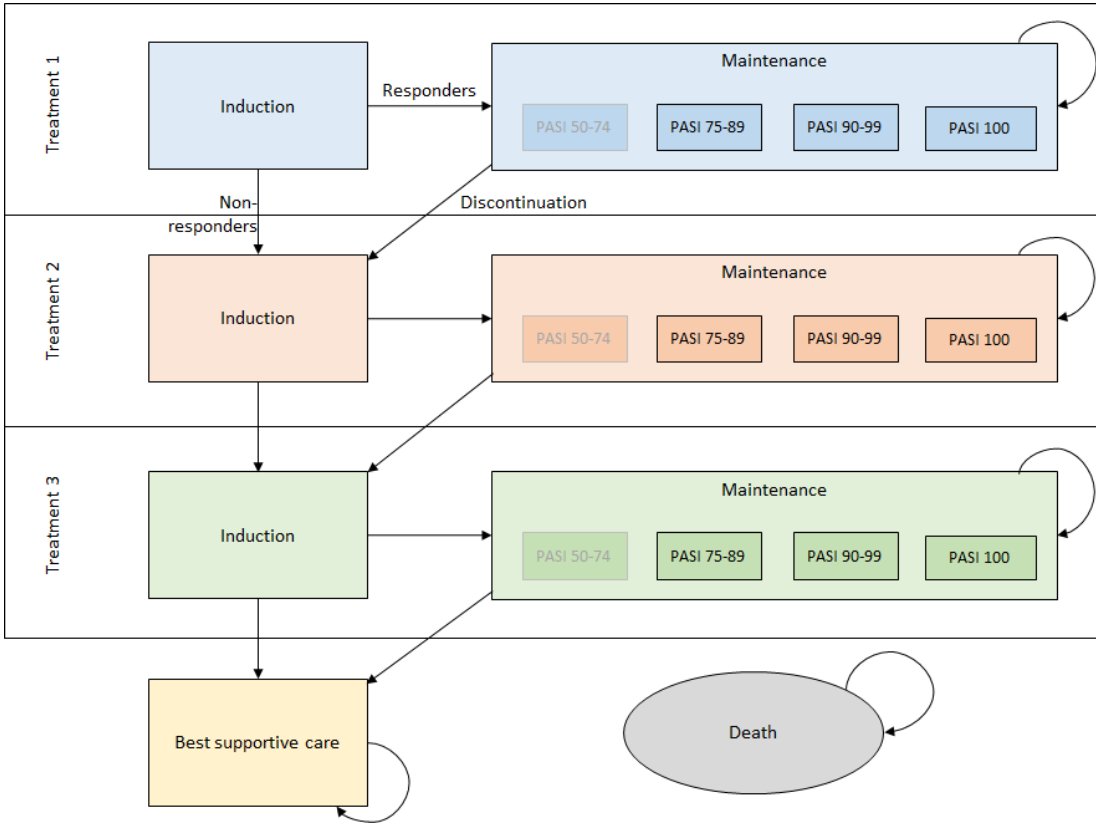
Based on advice from an English advisory board made up of clinical and health economic experts, as well as 2017 British Association of Dermatologists (BAD) guidance (31), ustekinumab was considered to be the most likely second-line therapy, with secukinumab used as a common third-line treatment (Table 5). Third-line use of infliximab and use of a single comparator followed by BSC were explored in scenario analyses.

Table 6 Comparator sequences – base case (B.3.2.5, page 116)

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

BSC, best supportive care; DMF, dimethyl fumarate

Figure 7 Schematic model diagram (B.3.2.2, Figure 29, page 110)



PASI, Psoriasis Area and Severity Index.

Model characteristics

Approach: Markov model.

Perspective: UK NHS and Personal Social Services.

Cycle length: 2 weeks.

Time horizon: 40 years.

Induction period: dependent on therapy.

Transition from induction therapy: patients with PASI 75 after induction transition to maintenance therapy; remainder transition to the next treatment in the sequence.

Transition from maintenance therapy: patients maintain their induction level of PASI response until discontinuation, when they transition to the next treatment in the sequence.

BSC: after three active therapies, patients initiate BSC, which is continued until the end of the modelled time horizon or death.

Death: death is an absorbing state to which patients can transition from any model state at any time.

A.11 Incorporating clinical evidence into the model

During the induction period, patients were distributed across five PASI response levels based on the results of the base-case NMA (see sections A.8 and B.2.9). The overlapping, nested PASI categories derived from the NMA were transformed into mutually exclusive categories at the reported cut-offs (0–49, 50–74, 75–89, 90–99, 100). A multinomial likelihood NMA setup with probit link function was used to simultaneously calculate the probability of PASI 50, 75, 90 and 100 responses and the relative risk between each comparison in the network (see section B.3.3.1, page 118.

Utility values for moderate-to-severe psoriasis and for the five categories of PASI response following treatment were calculated from EQ-5D results reported by patients in the AMAGINE-1 trial using a least squares regression model (see section B.3.4.1, page 123)

In the base-case analysis, treatment discontinuation was assumed to be the same for all therapies, with a constant annual probability of 18.7%, which was derived from the UK British Association of Dermatologists Biologic Interventions Register (BADBIR; see section B.3.3.1, page 119) (32). Drug class-specific discontinuation rates were explored in a scenario analysis. The approach to estimating discontinuation and the resulting probabilities were presented to an advisory board of clinicians and health economic experts who agreed that both were appropriate, as was the assumption not to differentiate between therapies in the base case.

The cost and HRQoL impact of serious infection was included in the model, with serious infection rates for ustekinumab, infliximab, etanercept, and adalimumab derived from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) study (33), and from AMAGINE-2 and AMAGINE-3 52-week data (see section B.3.3.1, page 120) (20). Other adverse events were included in a scenario analysis.

Life-expectancy estimates were derived from an analysis of General Practice Research Database data (13), which found an excess risk of death among patients with severe psoriasis compared with matched control individual – this hazard ratio was applied to age-dependent all-cause mortality rates obtained from UK life tables (34), and applied as a background risk of death to all patients (see section B.3.3.2, page 122). Psoriasis treatment was assumed not to have any effect on overall mortality.

A.12 Key model assumptions and inputs

Key model assumptions and inputs are summarised in Table 6.

Table 7 Key model assumptions and inputs

Model input	Source/assumption	Justification
Treatment effect (PASI responses) (B.3.3.1)	PASI responses were based on the results of the base-case NMA.	Head-to-head data for all of the comparators of interest are lacking. Therefore, a NMA is the most appropriate source of relative efficacy data.
Treatment effect (maintenance) (B.3.6.2)	Treatment effect was assumed to be maintained with ongoing treatment.	In the absence of long-term evidence on the maintenance of PASI responses, it was assumed that responses are sustained until discontinuation. Loss of response is assumed to be captured by discontinuation of therapy.
Treatment effect (prior biologic use) (B.3.3.1)	Treatment efficacy was assumed to be the same regardless of exposure to prior therapies.	The placement of a drug within a sequence is not assumed to have any impact on its efficacy. Results of subgroup analyses from the AMAGINE trials showed that the efficacy of brodalumab was similar in patients with and without exposure to prior therapies, a finding that is similar to evidence presented in previous TAs of psoriasis treatments.
Discontinuation rate (B.3.3.1)	Discontinuation was assumed to occur at a constant rate, based on data from the BADBIR registry.	UK registry data have shown that psoriasis patients on biologic therapies discontinue treatment over time, but evidence is mixed as to whether drug survival is different between therapies and whether it is different for first, second or later line treatments. Because the BADBIR registry found a lower rate of discontinuation with ustekinumab than with anti-TNF therapies (32), a scenario analysis was performed in which IL-inhibitors were assumed to have a lower annual probability of discontinuation than anti-TNF therapies. A second scenario varied discontinuation rates according to treatment line.
Treatment costs (B.3.5.1)	Drug acquisition costs were derived from the online version of MIMS (35). For infliximab, the base-case analysis includes wastage arising from the partial use of a vial. The cost of BSC was based on the literature.	The brodalumab cost incorporates a confidential PAS discount. Apremilast, ixekizumab and secukinumab were recommended by NICE under a PAS that applied a confidential discount to their list prices. The base-case analysis uses the list price for these drugs. Biosimilar etanercept and biosimilar infliximab are currently available in the UK: the formulation with the lowest cost was used in the base-case analysis. For infliximab, a scenario explored an alternative cost per mg approach (no wastage). Fonia *et al.* (2010) (36), has been recommended by NICE evidence review groups as the most plausible estimate of BSC resource use for the UK (30, 37, 38).
Administration and monitoring costs (B.3.5.1)	For infliximab, the cost of an IV infusion is included. For other therapies, no administration cost is applied.	Infliximab is administered as an IV infusion by a health care professional. The cost of IV administration was based on the mean of a consultant- and a non-consultant led non-admitted face-to-face follow-up appointment in 2015–2016 NHS reference costs (39). For other therapies, all patients were assumed to be able to self-administer subcutaneous injections, reflecting the expected zero cost to the NHS for injection support due to home-care and support schemes to be offered by LEO Pharma in line with other biologic manufacturers. Apremilast and DMF are given orally.

BADBIR, British Association of Dermatologists Biologic Interventions Register; DMF, dimethyl fumarate; IV, intravenous; MIMS, Monthly Index of Medical Specialties; NMA, network meta-analysis; PAS, patient access scheme; PASI, Psoriasis Area and Severity Index; TA, technology appraisal; TNF, tumour necrosis factor.

A.13 Base-case ICER (deterministic)

A summary of base-case cost-effectiveness results is presented in Table 7. In the fully incremental analysis, DMF (sequence 9), which was associated with the lowest total quality-adjusted life-years (QALYs) at the lowest cost, is the referent comparator. Brodalumab (sequence 1) is the first comparator sequence on the cost-effectiveness frontier and is associated with an incremental cost-effectiveness ratio (ICER) of £13,353 per QALY versus DMF (sequence 9). Ixekizumab (sequence 6) is most costly and generates 0.031 more QALYs than brodalumab (sequence 1), with an ICER of £894,010 per QALY. The adalimumab, ustekinumab, secukinumab and infliximab sequences are dominated by brodalumab, while apremilast and etanercept are extendedly dominated.

Table 8 Base-case results (deterministic) – B.3.7 (page 137)

Sequence	1st line	2nd line	3rd line	4th line	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) fully incremental	ICER (£/QALY): BRO sequence vs comparator
9	DMF	UST	SEC	BSC	£146,101	18.76	12.64	£0	0	0	-	£13,353
3	APR	UST	SEC	BSC	£149,236	18.76	12.72	£3,136	0	0.07	Extendedly dominated	£9,955
4	ETN	UST	SEC	BSC	£151,791	18.76	12.82	£5,690	0	0.18	Extendedly dominated	£7,145
2	ADA	UST	SEC	BSC	£156,036	18.76	13.10	£9,935	0	0.46	Dominated	Dominated
8	UST	ADA	SEC	BSC	£156,156	18.76	13.10	£10,055	0	0.46	Dominated	Dominated
7	SEC	UST	ADA	BSC	£161,524	18.76	13.11	£15,423	0	0.47	Dominated	Dominated
5	INF	UST	SEC	BSC	£172,212	18.76	13.23	£26,111	0	0.59	Dominated	Dominated
1	**BRO**	**UST**	**SEC**	**BSC**	£155,517	18.76	13.35	£9,416	0	0.71	£13,353	N/A
6	IXE	UST	SEC	BSC	£182,957	18.76	13.38	£36,857	0	0.74	£894,010	£894,010

ADA, adalimumab; APR, apremilast; BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ETN, etanercept 50 mg per week; ICER, incremental cost-effectiveness ratio; INF, infliximab; IXE, ixekizumab; LYG, life-years gained; QALYs, quality-adjusted life-years; SEC, secukinumab; UST, ustekinumab.

A.14 Probabilistic sensitivity analysis

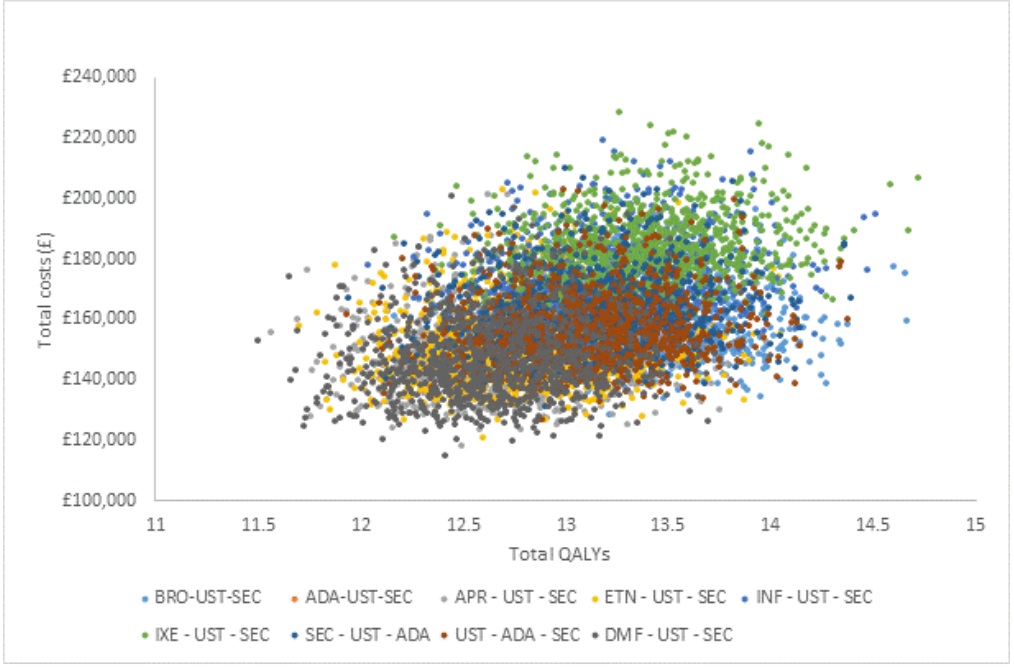
A probabilistic sensitivity (PSA) analysis was undertaken with 1,000 model simulations. Parameter distributions are described in the main evidence submission, sections B.3.6.1 (Table 56, page 133) and B.3.8.1 (page 138). A summary of the probabilistic results is presented in Table 8, and a graphical depiction of the simulations is shown in Figure 8. Overall, the PSA results were similar to those of the base-case analysis (B.3.8.1, page 138). The probability of brodalumab being cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 per QALY was 96% and 100%, respectively.

Table 9 Base-case results (probabilistic) – B.3.8 (page 138)

Sequence	Total QALYs		Total costs		Fully incremental ICER
	Mean	95% CrI	Mean	95% CrI	
9: DMF	12.65	11.90–13.43	£146,710	£126,074–£179,277	-
3: APR	12.72	11.98–13.49	£149,869	£129,584–£181,444	Extendedly dominated
4: ETN	12.83	12.09–13.61	£152,392	£132,811–£182,978	Extendedly dominated
2: ADA	13.11	12.39–13.86	£156,499	£137,975–£184,785	Dominated
8: UST	13.11	12.39–13.86	£156,632	£138,094–£184,930	Dominated
7: SEC	13.12	12.40–13.88	£162,055	£142,929–£190,655	Dominated
5: INF	13.24	12.52–13.99	£172,646	£153,935–£201,295	Dominated
1: BRO	**13.35**	**12.63–14.10**	**£155,966**	**£138,637–£182,568**	**£13,202**
6: IXE	13.38	12.67–14.15	£183,489	£165,010–£210,252	£903,712

ADA, adalimumab; APR, apremilast; BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ETN, etanercept 50 mg per week; ICER, incremental cost-effectiveness ratio; INF, infliximab; IXE, ixekizumab; LYG, life years gained; QALYs, quality-adjusted life years; SEC, secukinumab; UST, ustekinumab.

Figure 8 Scatterplot of probabilistic results (B.3.8.1, Figure 30, page 139)

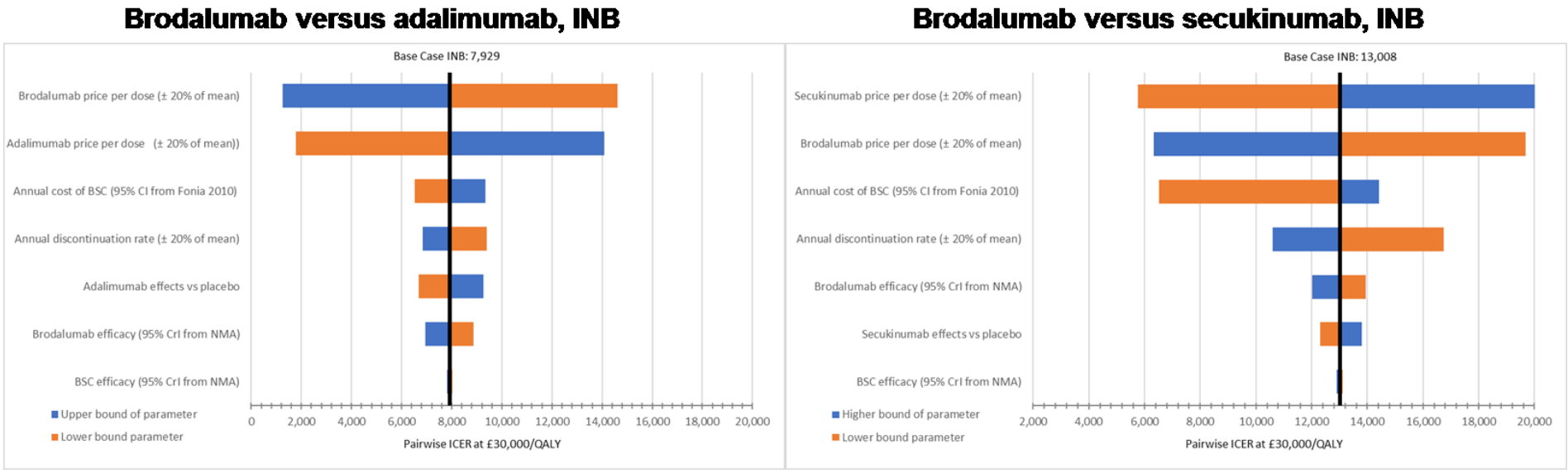


A.15 Key sensitivity and scenario analyses

Tornado diagrams for the brodalumab sequence versus the adalimumab and secukinumab sequences are shown in Figure 9. Tornado diagrams for brodalumab versus other treatment sequences are presented in the main evidence submission (section B.3.8.2, pages 142 and 143). An incremental net benefit (INB) approach was used for all comparators except DMF.

The main driver of the ICER/INB across pairwise comparisons is the acquisition cost of brodalumab and of the comparator therapy. The cost of BSC had an impact in the comparisons of brodalumab with DMF, apremilast, and secukinumab, but was less significant in the other comparisons (B.3.8.2, page 141). The effect of varying the efficacy of the comparator was largest in the comparison with DMF. The annual discontinuation rate had an impact on the comparisons of brodalumab with apremilast, etanercept, secukinumab, infliximab and ixekizumab.

Figure 9 Tornado diagram (B.3.8.2, Figure 32, pages 142 and 143)



The tornado diagram for brodalumab versus ustekinumab is very similar to that for brodalumab versus adalimumab.
BSC, best supportive care; ICER, incremental cost-effectiveness ratio; INB, incremental net benefit NMA, network meta-analysis; QALY, quality-adjusted life year.

Structural uncertainty was explored using multiple scenarios (section B.3.8.3, page 144) – the cost-effectiveness frontier was generally similar to the base-case analysis in the scenarios tested. Table 9 summarises the impact of key scenarios on the ICERs for brodalumab versus adalimumab, ustekinumab and secukinumab, which are recommended as first-line biological therapies in current BAD guidance (31).

Table 10 Key scenario analyses

Scenario and cross reference	Scenario detail	Brief rationale	Pairwise scenario ICER (impact on base-case pairwise ICERs)
Base case			vs DMF, £13,353 BRO dominates ADA, UST and SEC
Single treatment comparator (B.3.8.1 scenario 1, page 144)	One active therapy followed by BSC	Previous TAs (other than those for ixekizumab and DMF) modelled a single active treatment line.	vs BSC, £12,540 vs DMF, £16,451 (+£3,098) vs ADA, £3,805 BRO dominates UST and SEC
Prior biologic use increases discontinuation rate (B.3.8.1, scenario 4, page 146	Annual discontinuation for people with prior exposure increased by factor of 1.24	There is uncertainty regarding the effect of previous biologic use on treatment efficacy; a multiplier from the literature was applied to discontinuation rate to model an increase in secondary non-response (40).	vs DMF, £13,755 (+£402) BRO dominates ADA, UST and SEC
Drug class-specific discontinuation rate (B.3.8.1 scenario 5, page 148)	Annual discontinuation rates: anti-TNFs, 14.6%; IL-inhibitors, 7.3%	The BADBIR registry found a lower rate of discontinuation with ustekinumab than with anti-TNF therapies (32). Apremilast and DMF were assumed to be similar to anti-TNFs.	vs DMF, £3,495 (−£9,858) BRO dominates ADA, UST and SEC
Alternative utility values (B.3.8.1 scenario 8, page 150)	PASI response-specific utility gains from all patients in AMAGINE-1	Base-case utility was based on directly-elicited values from patients in AMAGINE-1 with baseline DLQI > 10. The scenario tests the use of utility values from the entire AMAGINE-1 population, including patients with baseline DLQI ≤ 10.	vs DMF, £16,444 (+£3,091) BRO dominates ADA, UST and SEC
Alternative values for efficacy of BSC (B.3.8.1 scenario 12, page 154)	A) 0% of patients using BSC achieve PASI 50; B) 65% achieve PASI 50 and 30% achieve PASI 75	There is uncertainty regarding the effectiveness of BSC. This scenario explored A) lower and B) higher effectiveness for BSC, based on literature values (41).	A) vs DMF, £12,244 (−£1,109) BRO dominates ADA, UST and SEC B) vs DMF, £19,694 (+£6,341) BRO dominates ADA, UST and SEC

ADA, adalimumab; BADBIR, British Association of Dermatologists Biologic Interventions Register; BRO, brodalumab; BSC, best supportive care; DLQI, Dermatology Life Quality Index; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; QALY, quality-adjusted life year; TA, technology appraisal; TNF, tumour necrosis factor.

A.16 Innovation

In addition to the utility gains associated with improvement in PASI score, the AMAGINE trials have demonstrated a number of benefits of brodalumab that may not be fully captured in the ICER calculation:

- In delivering complete skin clearance for more than half of patients (at 52 weeks), brodalumab represents a step-change in the management of moderate-to-severe psoriasis. The long-term HRQoL benefits of complete clearance of psoriasis symptoms may not be fully captured within the QALY calculation.
- Brodalumab is efficacious in the treatment of nail and scalp psoriasis, both of which are poorly represented in the PASI (131) and may not be adequately captured by the EQ-5D.
- Response to brodalumab treatment is rapid, with fewer induction doses required than some other biological therapies, potentially reducing budget uncertainty and providing an additional HRQoL benefit for patients.
- Use of brodalumab is associated with a sustained response to treatment, even if therapy is interrupted – this may lead to lower discontinuation rates with brodalumab compared with other therapies, which is not captured in the model.
- With a different mechanism of action, brodalumab provides an alternative choice within the IL-17 class.

For further information see section B.2.12 in the main submission (page 94).

A.18 Budget impact

The anticipated budget impact of brodalumab is summarised in Table 10.

Table 11 Budget impact – Company budget impact analysis submission

	Company estimate	Cross reference
Number of people in England who would have treatment	2018: 616 2019: 1,247 2020: 1,892 2021: 2,552 2022: 2,904	Company budget impact analysis submission Table 14, page 10.
Average treatment cost per person, list price	Year 1: £17,311 Year 2: £16,671	Company budget impact analysis submission Figure 5, page 21.
Estimated annual budget impact on the NHS in England, list price (PAS price)	2018: £4,965,408 ([redacted]) 2019: £10,047,716 ([redacted]) 2020: £15,246,924 ([redacted]) 2021: £18,343,609 ([redacted]) 2022: £17,812,976 ([redacted])	Company budget impact analysis submission Table 11, page 21 and Table 12, page 21.

PAS, patient access scheme.

A.19 Interpretation and conclusions of the evidence

The efficacy of brodalumab 210 mg Q2W for the treatment of moderate-to-severe psoriasis in adults was demonstrated in three phase 3 trials designed to include a typical moderate-severe psoriasis population: AMAGINE-1, AMAGINE-2 and AMAGINE-3. Brodalumab demonstrated rapid and sustained improvements in psoriasis symptoms and HRQoL compared with placebo and the active comparator ustekinumab, with a comparable safety profile.

Overall, clinical responses were highly consistent among the phase 3 trials, with 36.7–44.4% of patients treated with brodalumab 210 mg Q2W achieving PASI 100 at 12 weeks. The long-term HRQoL benefits of achieving completely clear skin may not be fully captured within the QALY calculation. In addition, brodalumab was efficacious in the treatment of nail and scalp psoriasis, both of which are poorly represented in the PASI and may not be adequately captured by the EQ-5D.

In addition to efficacy in patients receiving continuous therapy, the AMAGINE trials demonstrated the efficacy of brodalumab 210 mg Q2W administered after a prior biological therapy (ustekinumab) had failed to generate an adequate response, or after withdrawal of therapy.

In the economic analysis, the brodalumab–ustekinumab–secukinumab–BSC sequence had an ICER of £13,353 versus DMF–ustekinumab–secukinumab–BSC, the next most effective sequence on the cost-effectiveness frontier. The model, which was based on PASI data from a comprehensive NMA and directly-elicited utility values, was found to be robust in probabilistic and deterministic sensitivity analyses (ICERs vs DMF were £933–£30,074).

In conclusion, the evidence shows that brodalumab is likely to be an efficacious, cost-effective option for the treatment of moderate-to-severe plaque psoriasis. With a different mechanism of action, brodalumab provides an alternative choice within the IL-17 class for the treatment of adult patients who are candidates for systemic therapy, and for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated.

A.20 References

1. National Institute of Health and Care Excellence. Clinical Guideline 153. Psoriasis: assessment and management. [Updated 4 September 2017. Available from: https://www.nice.org.uk/guidance/cg153/resources/psoriasis-assessment-and-management-35109629621701. Accessed: 4 September 2017.]
2. Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence. Journal of Investigative Dermatology. 2013;133(2):377-85.
3. Springate DA, Parisi R, Kontopantelis E, Reeves D, Griffiths CEM, Ashcroft DM. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. The British Journal of Dermatology. 2017;176(3):650-8.
4. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, 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. Journal of the American Academy of Dermatology. 2008;58(5):826-50.
5. Leino M, Mustonen A, Mattila K, Koulu L, Tuominen R. Influence of Psoriasis on Household Chores and Time Spent on Skin Care at Home: A Questionnaire Study. Dermatology and Therapy. 2015;5(2):107-16.
6. 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. Archives of dermatology. 2001;137(3):280-4.
7. Lynde CW, Poulin Y, Guenther L, Jackson C. The burden of psoriasis in Canada: insights from the pSoriasis Knowledge IN Canada (SKIN) survey. Journal of cutaneous medicine and surgery. 2009;13(5):235-52.
8. Gowda S, Goldblum OM, McCall WV, Feldman SR. Factors affecting sleep quality in patients with psoriasis. Journal of the American Academy of Dermatology. 2010;63(1):114-23.
9. Anstey A, McAteer H, Kamath N, Percival F. Extending psychosocial assessment of patients with psoriasis in the UK, using a self-rateds, web-based survey. Clinical and experimental dermatology. 2012;37(7):735-40.
10. Feldman SR, Zhao Y, Shi L, Tran MH. Economic and Comorbidity Burden Among Patients with Moderate-to-Severe Psoriasis. Journal of managed care & specialty pharmacy. 2015;21(10):874-88.
11. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GB, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol. 2015;135(4):984-91.
12. Mehta NN, Yu Y, Pinnelas R, Krishnamoorthy P, Shin DB, Troxel AB, et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. The American journal of medicine. 2011;124(8):775.e1-6.
13. Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Archives of dermatology. 2007;143(12):1493-9.
14. Armstrong AW, Schupp C, Wu J, Bebo B. Quality of Life and Work Productivity Impairment among Psoriasis Patients: Findings from the National Psoriasis Foundation Survey Data 2003–2011. PLoS ONE. 2012;7(12):e52935.

15. Russo PAJ, Ilchef R, Cooper AJ. Psychiatric morbidity in psoriasis: A review. Australasian Journal of Dermatology. 2004;45(3):155-61.
16. Hrehorow E, Salomon J, Matusiak L, Reich A, Szepietowski JC. Patients with psoriasis feel stigmatized. Acta dermato-venereologica. 2012;92(1):67-72.
17. Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety and suicidality in patients with psoriasis: A population-based cohort study. Archives of dermatology. 2010;146(8):891-5.
18. Lynde CW, Poulin Y, Vender R, Bourcier M, Khalil S. Interleukin 17A: toward a new understanding of psoriasis pathogenesis. Journal of the American Academy of Dermatology. 2014;71(1):141-50.
19. 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.
20. 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.
21. Nakagawa H, Niiro H, Ootaki K. 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. Journal of dermatological science. 2016;81(1):44-52.
22. Papp KA, Leonardi C, Menter A, Ortonne J-P, Krueger JG, Kricorian G, et al. Brodalumab, an Anti–Interleukin-17–Receptor Antibody for Psoriasis. New England Journal of Medicine. 2012;366(13):1181-9.
23. Amgen Inc. A Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-2 (Clinical Study Report). 30 March 2015. Data on file.
24. Amgen Inc. Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-3 (Clinical Study Report). 27 March 2015. Data on file.
25. Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis - Protocol. N Engl J Med. 2015;373(14):1318-28.
26. Amgen Inc. A Phase 3 Study to Evaluate the Efficacy, Safety, and Effect of Withdrawal and Retreatment With Brodalumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-1 (Clinical Study Report). 15 May 2015. Data on file.
27. Strober B, Gordon K, Augustin M, Viswanathan H, Klekotka P, Milmont C, et al. Improvements in patient-reported outcomes (PROs) among moderate to severe plaque psoriasis patients treated with brodalumab: Results from AMAGINE-1. Journal of the American Academy of Dermatology. 2016;74(5):AB256.

28. Paul C, Barker J, Klekotka P, Milmont C, Viswanathan H, Nirula A, et al. Improvements in health-related quality of life measured by SF-36 and EQ-5D in patients with moderate to severe plaque psoriasis treated with brodalumab. Journal of the American Academy of Dermatology. 2016;74(5):AB256.
29. FDA. Clinical Outcome Assessment Review - Ixekizumab. 2016 [Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125521Orig1s000MedR.pdf. Accessed: 16 December 2016.]
30. National Institute for Health and Care Excellence. Single Technology Appraisal: Ixekizumab for treating moderate to severe plaque psoriasis [ID904] Committee Papers. [Internet]. London, UK: National Institute for Health and Care Excellence. 2016 [cited 2017 Jan 31]. Available from: https://www.nice.org.uk/guidance/GID-TA10063/documents/committee-papers-3. Accessed: 31 January.]
31. 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. British Journal of Dermatology. 2017:n/a-n/a.
32. Warren RB, Smith CH, Yiu ZZ, Ashcroft DM, Barker JN, 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(11):2632-40.
33. Kalb RE, Fiorentino DF, Lebwohl MG, et al. Risk of serious infection with biologic and systemic treatment of psoriasis: Results from the psoriasis longitudinal assessment and registry (psolar). JAMA dermatology. 2015;151(9):961-9.
34. Office for National Statistics. Life Expectancy at Birth and at Age 65 for the UK and Local Areas in England and Wales. 2015 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/interimlifetablesenglandandwales. Accessed: 5 September 2017.]
35. Monthly Index of Medical Specialties, August 2017 [Internet].
36. Fonia A, Jackson K, LeReun C, D.M. Grant, Barker JNWN, 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. British Journal of Dermatology. 2010;163 (4):807–16.
37. National Institute for Health and Care Excellence. Single Technology Appraisal: Secukinumab for the treatment of moderate to severe plaque psoriasis [TA350] Committee Papers. London, UK: National Institute for Health and Care Excellence. 2015 [cited 2017 31 Jan]. Available from: https://www.nice.org.uk/guidance/TA350/documents/secukinumab-for-treating-moderate-to-severe-plaque-psoriasis-committee-papers2. Accessed: 31 January.]
38. National Institute for Health and Care Excellence. Technology Appraisal Guidance: Dimethyl fumarate for treating moderate to severe plaque psoriasis [TA475] London, UK: National Institute for Health and Care Excellence. 2017 [Available from: https://www.nice.org.uk/guidance/ta475/resources/dimethyl-fumarate-for-treating-moderate-to-severe-plaque-psoriasis-pdf-82604967702469. Accessed: 6 September.]

39. NHS Reference Costs [Internet]. 2015–16.
40. 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):244-52.
41. Woods AL, Rutter KJ, Gardner LS, Lewis VJ, Saxena S, George SA, et al. Inpatient management of psoriasis: a multicentre service review to establish national admission standards. British association of dermatologists 2007;158:266-72.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Brodalumab for treating moderate to severe plaque psoriasis in adults [ID878]

Document B

Company evidence submission

November 2017

File name	Version	Contains confidential information	Date
Brodalumab STA [ID878] Section B [contains confidential information].docx	**1.2**	**Yes**	**17 November 2017**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Submission length excluding template and references: 148 pages.

Tables

Appendix tables

Figures

Appendix figures

Abbreviations

ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic Interventions Register
BCG	Bacillus Calmette-Guerin
BID	Twice daily
BSA	Body surface area
BSC	Best supportive care
C-CASA	Columbia-Classification Algorithm for Suicide Assessment
CCG	Clinical Commissioning Group
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CrI	Credible interval
CSR	Clinical study report
CUA	Cost–utility analysis
DIC	Deviance Information Criterion
DLQI	Dermatology Life Quality Index
EAS	Efficacy analysis set
EMA	European Medicines Agency
EQ-5D	EuroQol-5D questionnaire
ERG	Evidence Review Group
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GPRD	General Practice Research Database
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IGA	Investigator Global Assessment
IL	Interleukin
INB	Incremental net benefit
IQR	Interquartile range
IV	Intravenous
KM	Kaplan-Meier
LOCF	Last observation carried forward
LSM	Least squares mean
LY	Life-year
MACE	Major adverse cardiovascular events
MI	Multiple imputation
MIMS	Monthly Index of Medical Specialties
NA	Not applicable
NAPSI	Nail Psoriasis Severity Index
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMSC	Non-melanoma skin cancer
NRI	Non-responder imputation
NT	Not tested

OR	Odds ratio
PAS	Patient access scheme
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic
PK	Pharmacokinetic
PPD	Purified protein derivative
PsA	Psoriatic Arthritis
PSA	Probabilistic sensitivity analysis
PSI	Psoriasis Symptom Inventory
PSSI	Psoriasis Scalp Severity Index
PSSRU	Personal Social Services Research Unit
PUVA	Psoralen and ultraviolet A photochemotherapy
QALY	Quality-adjusted life-year
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
RCT	Randomised controlled trial
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SMQ	Standardised MedDRA Query
SOC	System organ class
sPGA	Static Physician's Global Assessment
STA	Single Technology Appraisal (NICE)
TA	Technology Appraisal (NICE)
TNF	Tumour necrosis factor
UME	Unrelated mean effects
WAC	Wholesale acquisition cost
WBC	White blood cell

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

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	Moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy, and for whom standard systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated	As per summary of product characteristics (SmPC) and anticipated placement in the treatment pathway
Intervention	Brodalumab	Brodalumab 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks	As per reference case and final label
Comparator(s)	If non-biologic systemic treatment or phototherapy is suitable: • Systemic non-biological therapies (including acitretin, ciclosporin, dimethyl fumarate (subject to ongoing NICE appraisal), fumaric acid esters, methotrexate) • Phototherapy with ultraviolet (UVB) radiation For people with severe or very severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated: • TNF-alpha inhibitors (etanercept, infliximab, adalimumab) • Ustekinumab • Secukinumab	For people with severe or very severe psoriasis for whom standard systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated: • TNF-alpha inhibitors (etanercept, infliximab, adalimumab) • Ustekinumab • Secukinumab • Apremilast • Ixekizumab • Dimethyl fumarate (subject to ongoing NICE appraisal) • Best supportive care	In clinical practice, brodalumab is likely to be offered at a similar place in the clinical pathway as existing NICE approved biological treatments, apremilast and dimethyl fumarate, i.e. after standard systemic therapies have failed, are contraindicated or are not tolerated. This is in line with the NICE pathway for the use of biologics in psoriasis (1). Based on this likely placement in the treatment pathway, the most appropriate comparators for brodalumab are other biologic treatments, apremilast and dimethyl fumarate , not standard systemic therapies (e.g. acitretin, ciclosporin, fumaric acid esters, methotrexate) or phototherapy.

	• Apremilast • Ixekizumab • Dimethyl fumarate (subject to ongoing NICE appraisal) • Best supportive care		
Outcomes	• Severity of psoriasis (including the Psoriasis Area Severity Index [PASI]) • Psoriasis symptoms on the face, scalp and nails • Mortality • Response rate • Relapse rate • Adverse effects of treatment • Health-related quality of life (including dermatology quality of life index [DLQI]).	• Severity of psoriasis (including the Psoriasis Area Severity Index [PASI]) • Psoriasis symptoms on the face, scalp and nails • Mortality • Response rate • Relapse rate • Adverse effects of treatment • Health-related quality of life (including dermatology quality of life index [DLQI]).	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • previous use of systemic non-biological therapy • previous use of biological therapy • severity of psoriasis (moderate, severe)	The following subgroups were analysed: • severity of psoriasis (moderate, severe, by PASI score) • impact of psoriasis (by DLQI score) • previous use of systemic non-biological therapy or phototherapy • previous use of systemic non-biological therapy • number of previous systemic therapies • systemic agent failure or contraindication • previous use of biological therapy • previous failure of biological therapy • previous use of anti-TNF therapy	All subgroups in scope were assessed; additional subgroups of potential relevance were also included

DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity index; Q2W, every 2 weeks.

B.1.2 Description of the technology being appraised

Appendix C includes the summary of product characteristics and the European public assessment report.

Table 2 Technology being appraised

UK approved name and brand name	Brodalumab (Kyntheum®)
Mechanism of action	Brodalumab is the first fully human immunoglobulin G2b monoclonal antibody with a high affinity for IL-17 receptor A
Marketing authorisation/CE mark status	Brodalumab (Kyntheum®) was granted a European marketing authorisation (EU/1/16/1155/001) on 17 July 2017
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Brodalumab (Kyntheum®) is indicated for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy
Method of administration and dosage	The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks
Additional tests or investigations	Brodalumab has a similar administration profile to other biological treatments available to NHS England patients; no additional tests or investigations are required
List price and average cost of a course of treatment	NHS list price: £1280 per pack of 2 syringes. Annual cost of treatment (list price): year 1, £17,280; subsequent years, £16,640
Patient access scheme (if applicable)	A confidential patient access scheme (PAS) has been agreed and approved by the Patient Access Scheme Liaison Unit (PASLU)/Department of Health. [redacted]

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

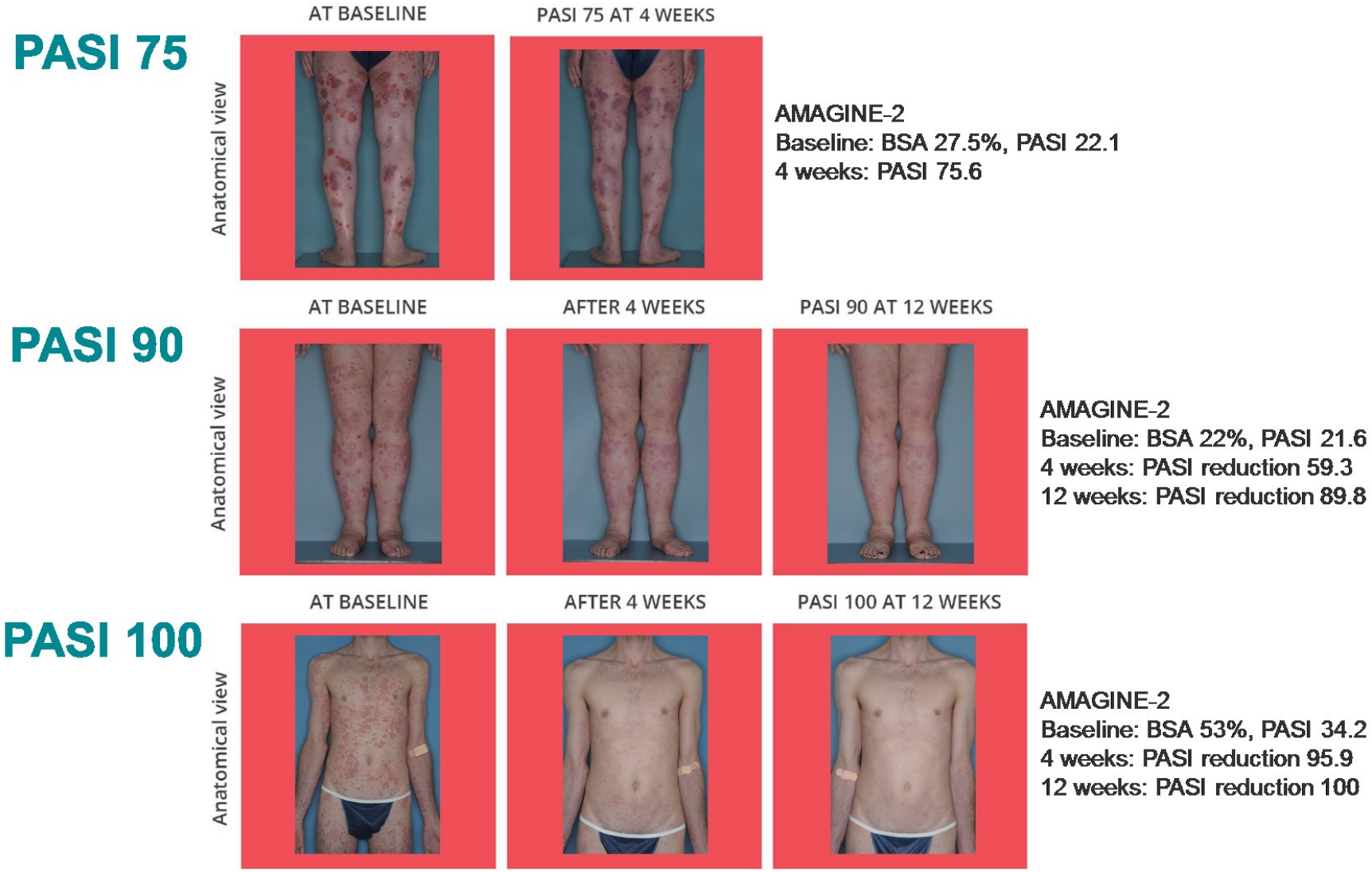
B.1.3.1 Disease overview

Psoriasis is a chronic, inflammatory, immune-mediated skin disorder which follows a relapsing–remitting pattern (2). Psoriasis affects men and women equally, and can occur at any age, with onset in the majority of cases occurring before 35 years of age (2, 3). The prevalence of psoriasis is higher among Caucasians than other ethnic groups (3). In the UK, psoriasis affects 3% of the population (4), of whom approximately 20% (corresponding to ~ 230,000 people in England) have moderate-to-severe disease (5).

There are five different forms of psoriasis: plaque, guttate, inverse, pustular, and erythrodermic (6). Chronic plaque psoriasis (psoriasis vulgaris) is the most common form, accounting for 90% of all cases (5). Common symptoms of chronic plaque psoriasis include scaling, itching, redness, tightness of the skin, bleeding and burning (Figure 1), which can affect sleep and physical functioning, and restrict activities of daily living and work productivity (7-11). Chronic plaque psoriasis is associated with comorbidities including other autoimmune diseases, hyperlipidaemia, hypertension, diabetes and depression (12, 13). In an analysis of the UK General Practice Research Database (GPRD), severe psoriasis was found to be a risk factor for major adverse cardiac events (hazard ratio, 1.53) after adjustment for traditional cardiovascular risk factors (age, gender, diabetes, hypertension, tobacco use and hyperlipidaemia) (14). Chronic plaque psoriasis is also associated with an increased risk of death – in another GPRD study, male and female patients with moderate-to-severe psoriasis died 3.5 and 4.4 years younger, respectively, than patients without psoriasis ($p < 0.001$), and a significant increase in mortality risk was found after adjustment for other risk factors (hazard ratio, 1.42) (15).

Chronic plaque psoriasis is associated with a significant impact on patients' health-related quality of life (HRQoL). Itching and scaling are typically the most distressing symptoms for patients, and most experience skin pain or discomfort (16, 17), leading to chronic sleep deprivation (10, 17). In addition to physical symptoms, the psychosocial impact of psoriasis can be devastating, with many patients suffering from isolation, stigmatisation, embarrassment, and difficulties in sexual relations (18-20). Overall, the HRQoL impact of psoriasis is comparable to that of other chronic health conditions such as heart disease, diabetes and arthritis (21-23), and can lead to profound psychological morbidity, reduced levels of employment and income, and increased risk of depression and anxiety (2, 13, 24). A UK GPRD study, including 149,998 patients with psoriasis, has estimated that each year more than 10,400 diagnoses of depression, 7100 diagnoses of anxiety and 350 diagnoses of suicidality are attributable to psoriasis. The risk of depression is particularly high among patients with severe psoriasis (hazard ratio, 1.72 versus controls, compared with 1.38 for patients with mild psoriasis) (24).

Figure 1 Examples of psoriasis and improvement with brodalumab treatment

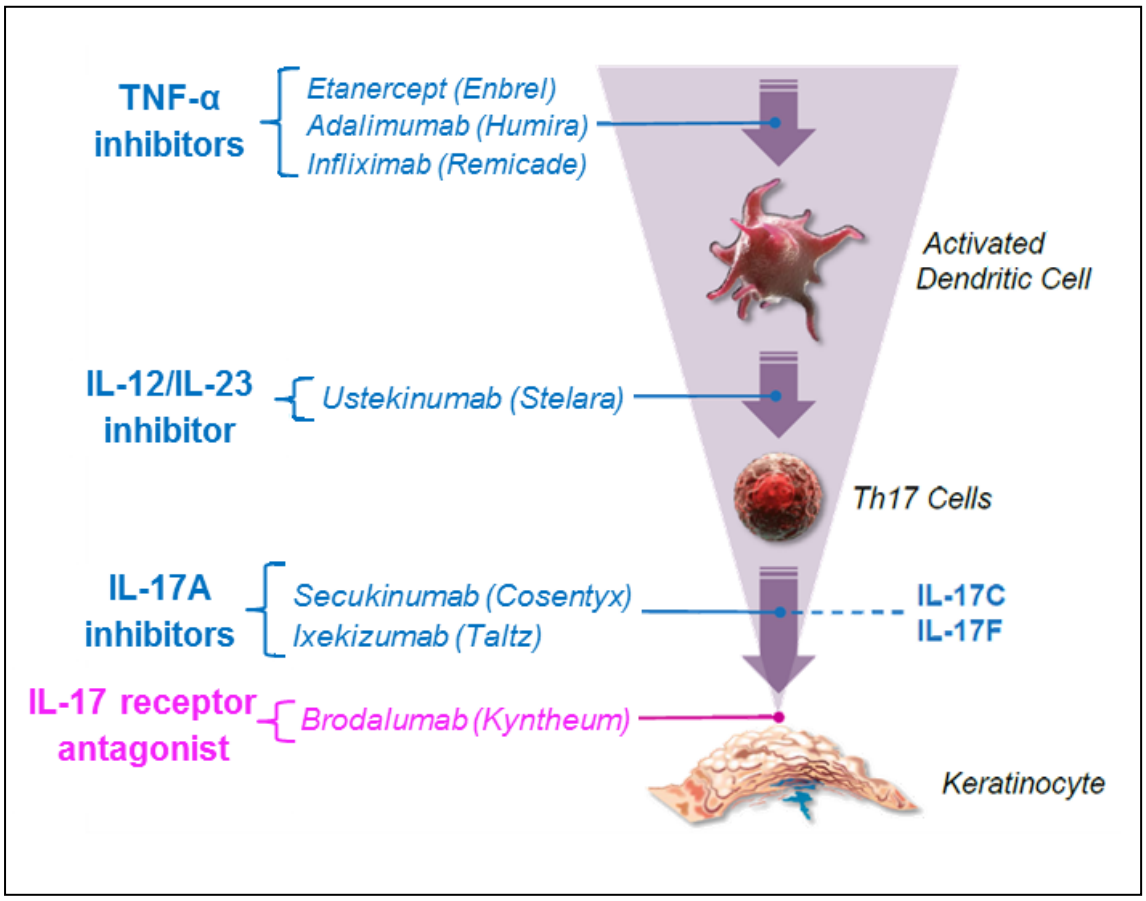


BSA, body surface area; PASI, Psoriasis Area and Severity Index.
Source: LEO Pharma data on file.

B.1.3.2 IL-17–Th17 signalling pathway

Psoriasis is primarily mediated by T helper (Th) cells, which produce cytokines that lead to keratinocyte proliferation and skin inflammation. The interleukin-23 (IL-23)/Th17 pathway plays a central role in amplifying the immune response, leading to excess production of the primary Th17 cell effector cytokine IL-17A. Patients with psoriasis have significantly higher levels of IL-17 than people without psoriasis, and psoriatic skin may have IL-17 levels 30-fold higher than non-psoriatic skin (25-28). IL-17 activity directly and indirectly drives key inflammatory circuits and induces activation of keratinocytes (25). Therefore, the IL-17 pathway (Figure 2) plays a central role in psoriasis pathogenesis and blocking the effects on keratinocytes of IL-17A, the most critical Th cell-derived cytokine, is a critical therapeutic goal (25).

Figure 2 IL-17 pathway and specific activity of brodalumab at IL-17 receptor



IL, interleukin; Th, T helper; TNF, tumour necrosis factor.
IL-17F is also secreted by Th17 calls, but the IL17A/A homodimer is 10 to 30 times more potent than the IL-17F/F homodimer in activating gene expression; the IL-17A/IL-17F heterodimer has intermediate potency. IL-17C is produced by epithelial cells.
Figure adapted from Lynde *et al.* 2014 (25).

B.1.3.3 Biological therapies for moderate-to-severe psoriasis

A number of biological therapies have been developed that target the IL-17–Th17 pathway (1, 29). First-generation biological therapies for psoriasis included the broadly acting anti-tumour necrosis factor (anti-TNF) agents adalimumab, etanercept and infliximab (1); these were followed by the interleukin (IL)-12/-23 inhibitor ustekinumab (1). Third-generation biological therapies for psoriasis include the targeted IL-17A inhibitors secukinumab and ixekizumab (1).

As biological therapies for psoriasis have developed, the focus has changed from upstream targets such as IL-23, which acts on Th17 cells, and TNF, which affects psoriasis through activation of dendritic cells as well as amplifying the effects of IL-17A via IL-22 (30), to more proximal targets which act closer to the keratinocyte (25).

The anti-TNF therapies and ustekinumab transformed the treatment of moderate-to-severe psoriasis, but the majority of patients do not achieve complete skin clearance with these medicines (31). In addition, many patients discontinue treatment due to loss of response over time or side effects (32-34); in the UK British Association of Dermatologists Biologic Interventions Register (BADBIR), 23% of patients being treated with a first biologic discontinued within 1 year, and 47% had done so by year 3 (33).

Recently, studies of secukinumab and ixekizumab have shown that for many patients targeting IL-17A activity has the potential to deliver higher response rates, including complete skin clearance, measured as a 100% improvement in PASI score (PASI 100) (1). PASI 100 is associated with greater improvement in symptom burden and HRQoL than lower levels of clearance (e.g. PASI 75; the difference between PASI 100 and PASI 75 is illustrated in Figure 1) (35, 36). With the high levels of efficacy demonstrated by recent therapies, PASI 100 may be the most appropriate patient-relevant endpoint (35).

B.1.3.4 Brodalumab mechanism of action

Brodalumab is a fully human monoclonal antibody (37). In contrast to secukinumab and ixekizumab, which target the IL-17A ligand (25), brodalumab targets the IL-17-receptor A (IL-17RA) (37). The first IL-17 inhibitor to act on the IL-17 receptor on keratinocytes and immune cells, brodalumab blocks the biological activity of the pro-inflammatory cytokines IL-17A, IL-17F, IL-17A/F heterodimer and IL-25, inhibiting the inflammation and clinical symptoms associated with psoriasis (25). With a mechanism of action different from other IL-17A inhibitors (Figure 2), brodalumab provides clinicians and patients with an additional alternative to existing biological therapies for the treatment of moderate-to-severe psoriasis in adults.

B.1.3.5 Clinical pathway of care for psoriasis

The NICE treatment pathway for psoriasis was updated in July 2017 (1). First-line treatment for mild psoriasis is topical therapy (1). Patients with more severe disease may require treatment with phototherapy or systemic non-biological therapies (typically methotrexate or ciclosporin). For a proportion of patients, systemic non-biological therapies will not provide

effective control of their psoriasis; for these patients, treatment with the phosphodiesterase 4 inhibitor apremilast, the anti-inflammatory agent dimethyl fumarate (DMF) or biological therapies may be needed. NICE recommends apremilast, DMF or systemic biological therapies adults with plaque psoriasis when (1):

- the disease is severe as defined by a total PASI score of ≥ 10 and a Dermatology Life Quality Index (DLQI) score of > 10 (see section B.2.3.1.5 for description of these instruments).
- the psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and phototherapy; or the person is intolerant of, or has a contraindication to, these treatments.

Infliximab is recommended only when the disease is very severe, as defined by a total PASI score of ≥ 20 and a DLQI score of > 18 (1).

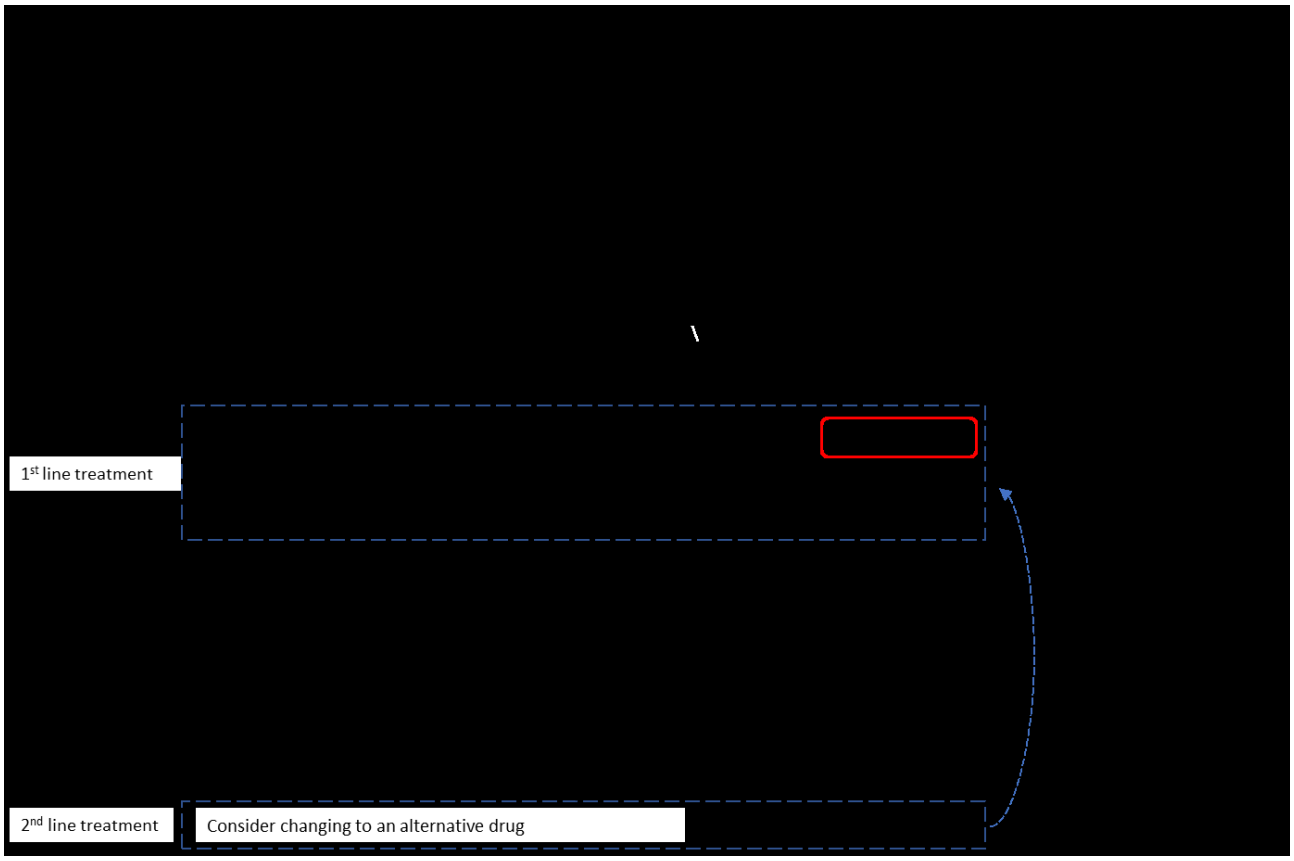
For each biological therapy, treatment should be discontinued in patients whose psoriasis has not responded adequately by 10 weeks (infliximab), 12 weeks (etanercept, ixekizumab, secukinumab) or 16 weeks (adalimumab, ustekinumab) (1). An adequate response is defined as either a 75% reduction in PASI score (PASI 75), or a 50% reduction in PASI score (PASI 50) and a five-point reduction in DLQI.

Physicians should consider switching patients to an alternative biological drug if their psoriasis has not responded adequately, if an initial response to therapy has been lost, or if the first biological drug cannot be tolerated or becomes contraindicated (1).

B.1.3.6 Proposed positioning of brodalumab in the current treatment pathway

Brodalumab should be considered as a treatment option for moderate-to-severe psoriasis, alongside the biological therapies adalimumab, etanercept, ixekizumab, secukinumab and ustekinumab, in patients whose psoriasis has not responded to standard systemic therapies or who are intolerant of, or have a contraindication to, these treatments (Figure 3).

Figure 3 Proposed position of brodalumab within the treatment pathway for patients with moderate-to-severe psoriasis, in accordance with NICE recommendations



DLQI, Dermatology Life Quality Index; DMF, dimethyl fumarate; IL, interleukin; IL-17 RA, IL-17-receptor A; PASI, Psoriasis Area Severity Index; TNF, tumour necrosis factor.

B.1.4 Equality considerations

An audit in the UK has suggested that there are wide variations in how psoriasis is treated in the adult population, including access to specialist treatments and biological therapy (38). Evidence suggests that older patients are less likely to receive biological treatments compared to younger patients. An increase in age of 30 years leads to a 61.3–67.6% decrease in the likelihood of receiving access to biological treatments, after controlling for covariates. It is currently not clear what the causes of this trend are, but economics, patient preferences, and prescriber wariness may all be contributing factors (39).

It is not anticipated that this appraisal will exclude from consideration any people protected by the equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

Summary

Clinical efficacy

Clinical trial evidence

- The efficacy and safety of brodalumab 210 mg every 2 weeks (Q2W) for the treatment of moderate-to-severe plaque psoriasis in adults has been investigated in three pivotal, double-blind, phase 3, randomised controlled trials (RCTs), AMAGINE-1, AMAGINE-2 and AMAGINE-3, which included a total of 4,373 patients (40, 41).
- All three AMAGINE studies compared brodalumab with placebo; the identical AMAGINE-2 and AMAGINE-3 trials also compared brodalumab with ustekinumab.
- The primary active-controlled endpoint in AMAGINE-2 and AMAGINE-3 was the proportion of patients treated with the licensed dose of brodalumab (210 mg Q2W; N = 612 and N = 624 in AMAGINE-2 and AMAGINE-3, respectively) achieving PASI 100 at week 12, compared with ustekinumab (weight-based dosing: (≤ 100 kg, 45 mg; > 100 kg, 90 mg; N = 300 and N = 313 in AMAGINE-2 and AMAGINE-3, respectively).
- The co-primary placebo-controlled endpoints in AMAGINE-2 and AMAGINE-3 were the proportions of patients treated with brodalumab 210 mg Q2W with a PASI 75 response, and with a static Physician's Global Assessment (sPGA) response (clear [0] or almost clear [1]), compared with placebo (N = 309 and N = 315 in AMAGINE-2 and AMAGINE-3, respectively) at week 12.
- PASI 75 response and sPGA response at week 12 were the co-primary placebo-controlled endpoints in AMAGINE-1 (brodalumab 210 mg Q2W, N = 222; placebo, N = 220).

Psoriasis clearance

- All three RCTs met their primary endpoints.
    - In AMAGINE-2 and AMAGINE-3, approximately twice as many patients treated with brodalumab 210 mg Q2W achieved PASI 100 at week 12 compared with ustekinumab (brodalumab, 44% and 37% in AMAGINE-2 and AMAGINE-3, respectively; ustekinumab, 22% and 19%; $p < 0.001$). In addition, most patients treated with brodalumab 210 mg Q2W achieved PASI 75 at week 12 (86% and 85% vs 70% and 69% with ustekinumab; $p < 0.001$).
    - In all three AMAGINE trials, significantly higher rates of PASI 75 response and sPGA response were achieved at week 12 with brodalumab 210 mg Q2W than with placebo (all $p < 0.001$).
- Onset of brodalumab efficacy was rapid: compared with ustekinumab in AMAGINE-2 and AMAGINE-3, statistically significant differences in PASI 100 response were demonstrated at week 4, and statistically significantly higher PASI 75 response rates were seen as early as week 1.
- Clinical response to brodalumab was maintained to week 52 in the AMAGINE-2 and AMAGINE-3 trials, with the majority of patients treated with constant brodalumab 210 mg Q2W achieving PASI 100 (56% and 53%; non-responder imputation [NRI]). Among the 20% of patients who switched to brodalumab 210 mg Q2W due to an inadequate response on ustekinumab at week 16 (sPGA ≥ 3 or

persistent sPGA scores of 2 over ≥ 4 weeks; 55 of 300 and 69 of 313), most (91% and 82%) went on to achieve PASI 75 at week 52.

- In AMAGINE-1 (N = 661), 42% of patients treated with the licensed dose of brodalumab (210 mg Q2W; N = 222) had a PASI 100 response at week 12. Among patients who had an sPGA response (0 or 1) at week 12 and were re-randomised to continue brodalumab 210 mg Q2W (N = 83), 67% had completely clear skin (PASI 100) at week 52 (NRI).
- A total of 84 patients in AMAGINE-1 had an sPGA response (0 or 1) at week 12 and were re-randomised to placebo. Of these, 79 experienced a return of disease (sPGA ≥ 3) during the withdrawal phase and were re-treated with brodalumab 210 mg Q2W. Almost all of these patients (97%) regained an sPGA response (0 or 1) after 12 weeks.
- In all three trials, responses to brodalumab 210 mg Q2W during the open-label extension phase were consistent with the results at 52 weeks, with PASI and sPGA responses maintained to week 108/120.

HRQoL

- Treatment with brodalumab 210 mg Q2W was associated with an increased likelihood versus ustekinumab of psoriasis no longer having an effect on a patient's life, as assessed with the DLQI; 61% and 59% of patients in the brodalumab 210 mg Q2W groups in AMAGINE-2 and AMAGINE-3, respectively, had DLQI scores of 0 or 1 at week 12, compared with 44% in both ustekinumab groups).
- At week 12 in AMAGINE-1, there was a statistically significant and clinically relevant difference in mean EQ-5D score between the brodalumab 210 mg Q2W and placebo groups (0.85 vs 0.61; $p < 0.001$).
- In addition, evidence from AMAGINE-1 demonstrated statistically significant reductions in Hospital Anxiety and Depression Scale (HADS) depression and anxiety scores versus placebo.

Subgroup analyses

- The results of subgroup analyses of the AMAGINE trials demonstrated that brodalumab 210 mg Q2W was significantly more efficacious than placebo and ustekinumab regardless of disease severity or prior exposure to systemic therapy, phototherapy and biological therapy.

Network meta-analysis

- Head-to-head RCTs between all comparators specified in the NICE scope have not been conducted; therefore, a network meta-analysis (NMA) was undertaken to estimate the relative efficacy between these treatments.
- The NMA results showed brodalumab 210 mg Q2W to be statistically significantly more efficacious than adalimumab 40 mg Q2W, apremilast 30 mg BID, etanercept 50 mg weekly, infliximab 5 mg/kg, secukinumab 300 mg, ustekinumab (45 mg, 90 mg, and dosing as per label) and DMF after 10–16 weeks of induction therapy.
- The efficacy of brodalumab 210 mg Q2W was not significantly different from that of ixekizumab 80 mg Q2W.

Safety

- The overall safety profile of brodalumab 210 mg Q2W in the AMAGINE-2 and AMAGINE-3 phase 3 RCTs was comparable to that of ustekinumab.
- In all three AMAGINE trials, the frequency of serious adverse events and events leading to discontinuation of the study or study medication was low, and was similar across randomised groups in both induction and maintenance phases.
- Overall, the most common adverse event during the induction phase of the AMAGINE trials was nasopharyngitis. Injection site reactions were the most common adverse event of interest; across the three studies, these occurred at a similar frequency in the brodalumab 210 mg Q2W, ustekinumab and placebo groups.
- Other than injection site reactions, *Candida* infections were the most common adverse event of interest over 52 weeks in the brodalumab 210 mg Q2W group; all of the infections were graded as mild or moderate, and none was systemic.
- Anti-drug antibodies were rare, with non-neutralising anti-brodalumab antibodies detected in 2% of patients; no patient had neutralising antibodies or a loss of efficacy or adverse events due to anti-drug antibodies.
- A small proportion of patients in the AMAGINE trials experienced suicidal ideation, and in total there were four completed suicides; however, no causal relationship has been established between brodalumab and suicidal ideation and behaviour.
    - An independent analysis conducted by the FDA Division of Epidemiology found similar levels of suicidal ideation and behaviour events with brodalumab, apremilast, ixekizumab, and infliximab.
    - Several studies have shown patients with moderate-to-severe psoriasis to be at significantly increased risk of clinical depression, anxiety and suicidal ideation.
    - The event rate for completed suicides in the brodalumab psoriasis programme was 0.04 (95% CI: 0.01 to 0.11) per 100 patient-years, compared with an overall event rate of 0.03 (95% CI: 0.01 to 0.06) per 100 patient-years observed in external trials and registry data for other biological agents and apremilast.
    - The AMAGINE trials did not exclude patients who might have an elevated risk of suicidal ideation and behaviour (due to history of depression, substance abuse, or prior history of suicidal behaviour); nevertheless, the data suggest that the risk of suicidal ideation and behaviour with brodalumab is no higher than that seen with other biological therapies.

B.2.1 Identification and selection of relevant studies

Identification and selection of relevant clinical evidence is described in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Brodalumab has been investigated for the treatment of moderate-to-severe plaque psoriasis in three phase 3 randomised controlled trials (RCTs): AMAGINE-1 (NCT01708590), AMAGINE-2 (NCT01708603) and AMAGINE-3 (NCT01708629) (Table 3). AMAGINE-2 and AMAGINE-3 were identical multicentre, international, active-controlled trials which compared the efficacy and safety of brodalumab with ustekinumab and placebo – these trials form the

main source of evidence in this submission. Supporting evidence of the effect of brodalumab is taken from AMAGINE-1, a multicentre, international, phase 3 placebo-controlled trial (41). All three AMAGINE trials were included in the network meta-analysis (NMA) that was used in the economic model (see section B.3).

The main source of data from AMAGINE-2 and AMAGINE-3 is the primary study publication (40), with additional data derived from the study protocol (published as an appendix to the primary study publication (42)) and clinical study reports (CSRs) (43, 44). The main source of data from AMAGINE-1 is the primary study publication (41, 45), with additional data derived from additional analyses published as abstracts (46, 47) and a CSR (48). Data from the open-label extension phase are derived from CSRs (45, 49, 50).

Two additional phase 2 studies of brodalumab were identified through the systematic review (51, 52). Because data are available from the three phase 3 AMAGINE trials, the phase 2 studies will not be described in detail in this submission. For completeness, they are included in the NMA presented in section B.2.9.

The data cut-off dates for the primary analysis were 12 March 2014 (AMAGINE-1), 22 September 2014 (AMAGINE-2) and 30 August 2014 (AMAGINE-3) – all 12-week and 52-week data presented in this submission correspond to this analysis. Commercial-in-confidence data that are not yet published are highlighted blue and underlined in the text.

Table 3 Clinical effectiveness evidence

Study	**AMAGINE-2 and AMAGINE-3**				
Study design	Multicentre, randomised, double-blind, placebo- and active comparator-controlled, parallel-group phase 3 trials with 12-week induction phase and 40-week maintenance phase.				
Population	Adults aged 18 to 75 years who were candidates for biological therapy for stable moderate-to-severe plaque psoriasis of at least 6 months' duration and who had a PASI score of 12 or higher, an sPGA score of 3 or higher, and involvement of 10% or more of the body surface area.				
Intervention(s)	Brodalumab 210 mg Q2W or brodalumab 140 mg Q2W [a]				
Comparator(s)	Ustekinumab or 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	Studies provide evidence of the efficacy of brodalumab 210 mg Q2W and were included in the network meta-analysis used in the economic model.				
Reported outcomes specified in the decision problem	**PASI 100, PASI 90 and PASI 75 response rates.** Improvement in DLQI score. Improvement in NAPSI score (nail involvement)				
All other reported outcomes	sPGA response PSI response				

Study	AMAGINE-1				
Study design	Multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trial with 12-week induction phase and 40-week maintenance phase.				
Population	Adults aged 18 to 75 years who were candidates for biological therapy for stable moderate-to-severe plaque psoriasis of at least 6 months' duration and who had a PASI score of 12 or higher, an sPGA score of 3 or higher, and involvement of 10% or more of the body surface area.				
Intervention(s)	Brodalumab 210 mg Q2W or brodalumab 140 mg Q2W [a]				
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	Study provides evidence of the efficacy of brodalumab 210 mg Q2W and was included in the network meta-analysis used in the economic model.				
Reported outcomes specified in the decision problem	**PASI 100, PASI 90 and PASI 75 response rates** Improvement in DLQI score. Improvement in PSSI score (scalp involvement) **EQ-5D utility values**				
All other reported outcomes	sPGA response PSI response Change in HADS scores				

[a] Brodalumab 140 mg Q2W is outside the proposed label for brodalumab in the treatment of moderate-to-severe plaque psoriasis; these results are not described in detail in this submission, but are summarised in Appendix L and published in Lebwohl *et al.* 2015 (40) and Papp *et al.* 2016 (41).
Sources: Lebwohl *et al.* 2015 (40), Papp *et al.* 2016 (41).
DLQI, Dermatology Life Quality Index; EQ-5D, EuroQol-5D questionnaire; HADS, Hospital Anxiety and Depression Scale; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; PSSI, Psoriasis Scalp Severity Index; sPGA, static Physician's Global Assessment; Q2W, every 2 weeks.

Patients in AMAGINE-1, AMAGINE-2 and AMAGINE-3 were eligible to enter an open-label extension phase, which was planned to last a further 4 years. All three AMAGINE trials were terminated on 22 May 2015 (53), and extension phase data are therefore reported at 120 weeks (AMAGINE-1 and AMAGINE-2) and 108 weeks (AMAGINE-3) (45, 49, 50).

The AMAGINE extension study was not used to populate the economic model but is included in sections 2.2 to 2.6. The results of this study provide additional evidence for the long-term efficacy and safety of brodalumab 210 mg Q2W. This study was not included in the economic model because of its open-label, uncontrolled design.

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

B.2.3.1 Methodology

B.2.3.1.1 Study design and interventions

AMAGINE-2 and AMAGINE-3

AMAGINE-2 and AMAGINE-3 were multicentre, randomised, double-blind, placebo- and active comparator-controlled, parallel-group phase 3 trials comparing brodalumab 210 mg, brodalumab 140 mg, ustekinumab and placebo (40). The primary aims were to evaluate the superiority of brodalumab over ustekinumab and placebo. Only brodalumab 210 mg every 2 weeks (Q2W) is included in the label (54, 55); therefore, results for other doses are not described in detail in this submission (results for brodalumab 140 mg Q2W are summarised in Appendix L and were published in Lebwohl *et al.* 2015 (40)).

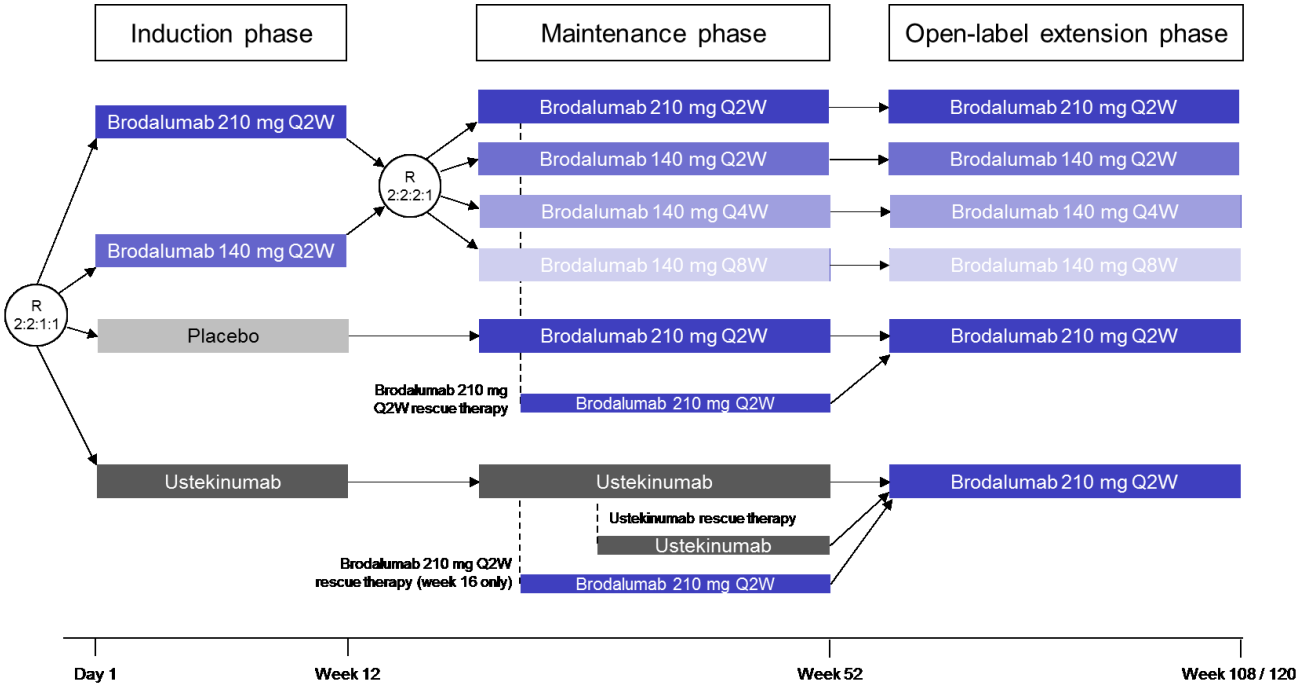
Both AMAGINE-2 and AMAGINE-3 included a 12-week induction phase and a 40-week maintenance phase (Figure 4). Patients were randomly assigned in a 2:2:1:1 ratio to receive brodalumab at a dose of 210 mg or 140 mg (subcutaneous injection on day 1 and weeks 1, 2, 4, 6, 8, and 10); ustekinumab (subcutaneous injection of 45 mg for patients with a body weight ≤ 100 kg and 90 mg for patients with a body weight > 100 kg, on day 1, week 4 and every 12 weeks [Q12W] thereafter); or placebo (subcutaneous injection on day 1 and weeks 1, 2, 4, 6, 8, and 10) (40).

At the week 12 visit, patients originally randomised to brodalumab were re-randomised 2:2:2:1 to receive brodalumab 210 mg every 2 weeks (Q2W), brodalumab 140 mg Q2W, brodalumab 140 mg every 4 weeks (Q4W), or brodalumab 140 mg every 8 weeks (Q8W). Patients originally randomised to ustekinumab continued to receive ustekinumab. Patients originally randomised to receive placebo began receiving brodalumab 210 mg Q2W (40).

Both AMAGINE-2 and AMAGINE-3 were double-blind, double-dummy studies. Patients received placebo injections in place of brodalumab or ustekinumab, as appropriate for each randomly assigned study group (because patients receiving brodalumab 210 mg received two injections of investigational product, those receiving brodalumab 140 mg received one brodalumab injection and one placebo injection) (42). Original and re-randomised treatment assignments remained blinded until week 52 (patients receiving ustekinumab every 12 weeks in the maintenance phase received placebo at 2-weekly visits to maintain blinding) (42). Rescue treatment was blinded throughout the maintenance phase (40).

At week 52, patients treated with ustekinumab were switched to receive brodalumab 210 mg Q2W during the open-label extension phase. Patients receiving brodalumab continued to receive brodalumab at the same maintenance or rescue dose (49, 50).

Figure 4 Study design – AMAGINE-2 and AMAGINE-3



R, randomisation; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks.
Source: Lebwohl *et al.* 2015 (40).

AMAGINE-1

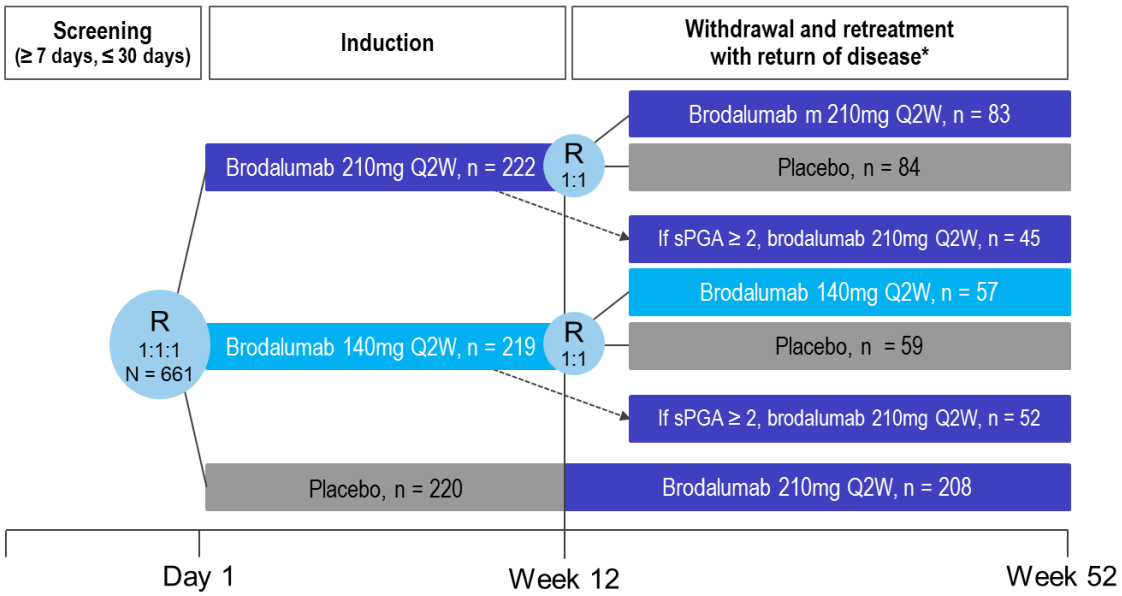
AMAGINE-1 was a 52-week, multicentre, randomised, double-blind phase 3 trial comparing brodalumab 210 mg Q2W, brodalumab 140 mg Q2W and placebo (41). Only brodalumab 210 mg Q2W is included in the label (54, 55); therefore, results for other doses are not described in detail in this submission (results for brodalumab 140 mg were published in Papp *et al.* 2016 (40)).

Patients were randomised 1:1:1 to brodalumab 140 mg Q2W, brodalumab 210 mg Q2W or placebo (Figure 5). At week 12, patients randomised to brodalumab who had an sPGA response (clear [0] or almost clear [1]) were re-randomised 1:1 to their induction dose of brodalumab or placebo ('withdrawal'). All other patients received brodalumab 210 mg Q2W. Patients in the withdrawal phase who experienced return of disease (sPGA ≥ 3) between weeks 16 and 52 were re-treated with their induction dose of brodalumab (41).

The co-primary endpoints in AMAGINE-1 were the proportion of patients achieving PASI 75 at week 12, and the proportion of patients achieving an sPGA response (clear [0] or almost clear [1]) at week 12. Key secondary endpoints were the proportion of patients with a PASI 100 response, an sPGA score of 0 and a Psoriasis Symptom Inventory (PSI) response at week 12, and the proportion achieving an sPGA response at week 52 (41).

After week 52, patients receiving brodalumab in AMAGINE-1 continued to receive brodalumab at the same maintenance or rescue dose during the open-label extension phase (45).

Figure 5 AMAGINE-1 study design



R, randomisation; Q2W, every 2 weeks; sPGA, static Physician's Global Assessment.

B.2.3.1.2 Randomisation and blinding

AMAGINE-2 and AMAGINE-3

In AMAGINE-2 and AMAGINE-3, initial randomisation lists were generated using a permuted block design stratified by baseline body weight (≤ 100 kg or > 100 kg), geographic region, and previous use of biological agents; enrolment of patients with previous biologic use was capped at 50% of each study population. Re-randomisation at week 12 was stratified by week 12 total body weight (≤ 100 kg or > 100 kg), induction regimen, and week 12 response (sPGA 0 vs sPGA ≥ 1) (40).

Both AMAGINE-2 and AMAGINE-3 were double-blind, double-dummy studies. Patients received placebo injections in place of brodalumab or ustekinumab, as appropriate for each randomly assigned study group (because patients receiving brodalumab 210 mg received two injections of investigational product, those receiving brodalumab 140 mg received one brodalumab injection and one placebo injection) (42). Original and re-randomised treatment assignments remained blinded until week 52 (patients receiving ustekinumab every 12 weeks in the maintenance phase received placebo at 2-weekly visits to maintain blinding) (42). Rescue treatment was blinded throughout the maintenance phase (40).

AMAGINE-1

Patients were randomised at baseline by an interactive voice response system to receive brodalumab 210 mg Q2W, brodalumab 140 mg Q2W or placebo, stratified by baseline body weight (≤ 100 kg or > 100 kg), geographic region, and previous use of biological agents; enrolment of patients with previous biologic use was capped at 50% of the study population. Re-randomisation at week 12 was stratified by week 12 total body weight (≤ 100 kg or > 100 kg), induction regimen, and week 12 response (sPGA 0 vs sPGA ≥ 1) (41).

Randomisations remained blinded to all patients and investigators and the clinical study team until the data through week 52 were finalised. Throughout the study, patients received placebo as needed to maintain the blind until it was broken (41).

B.2.3.1.3 Eligibility criteria

Adults aged 18 to 75 years who were candidates for biological therapy for stable moderate-to-severe plaque psoriasis of at least 6 months' duration were eligible if they had a PASI score of 12 or higher, an sPGA score of 3 or higher, and involvement of 10% or more of the body surface area. Patients with psoriatic arthritis were not excluded.

Patients with medical conditions that could potentially prevent them from completing the study or that could interfere with the interpretation of results were excluded. Full inclusion and exclusion criteria are listed in Table 4. Patients using other therapies for psoriasis were excluded from the trials unless the washout periods listed in Table 5 were completed before the first dose of investigational product was administered. Patients who might have an elevated risk of suicidal ideation and behaviour (due to history of depression, substance abuse, or prior history of suicidal behaviour) were not excluded (40, 41).

Table 4 Inclusion and exclusion criteria in the AMAGINE studies

Inclusion Criteria

- Patient has provided informed consent.
- Patient is ≥ 18 and ≤ 75 years of age at time of screening.
- Patient has had stable moderate-to-severe plaque psoriasis for at least 6 months before first dose of the investigative product (e.g., no morphology changes or significant flares of disease activity in the opinion of the investigator).
- Patient must be considered, in the opinion of the investigator, to be a suitable candidate for treatment with a biologic per regional labelling.
- Patient has involved BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ 3 at screening and at baseline.
- For women (except those surgically sterile or at least 2 years postmenopausal, with postmenopausal status confirmed by FSH in the postmenopausal range): a negative serum pregnancy test during screening and a negative urine pregnancy test at baseline.
- Patient has no known history of active tuberculosis.
- Patient has a negative test for tuberculosis during screening defined as either:
  - negative PPD (< 5 mm of induration at 48 to 72 hours after test is placed) OR
  - negative Quantiferon test.
- Patients with a positive PPD and a history of BCG vaccination are allowed with a negative Quantiferon test.
- Patients with a positive PPD test (without a history of BCG vaccination) or patients with a positive or indeterminate Quantiferon test are allowed if they have all of the following:
  - no symptoms per tuberculosis worksheet provided by Amgen
  - documented history of a completed course of adequate prophylaxis (per local standard of care)
  - no known exposure to a case of active tuberculosis after most recent prophylaxis
  - no evidence of active tuberculosis on chest radiograph within 3 months prior to the first dose of the investigative product.

Exclusion Criteria

- Patient diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions at the time of the screening visit (e.g., eczema) that would interfere with evaluations of the effect of the investigative product on psoriasis.
- Patient has a planned surgical intervention between baseline and the week 52 evaluation.
- Patient has an active infection or history of infections as follows:
    - any active infection for which systemic anti-infectives were used within 28 days prior to first dose of investigative product
    - a serious infection, defined as requiring hospitalisation or intravenous anti-infectives within 8 weeks prior to the first dose of investigative product
    - recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the patient.
- Patient has any systemic disease (e.g., renal failure, heart failure, hypertension, liver disease, diabetes, anaemia) considered by the investigator to be clinically significant and uncontrolled.
- Patient has known history of Crohn's disease.
- Patient has known history of hepatitis B, hepatitis C, or human immunodeficiency virus.
- Patient had myocardial infarction or unstable angina pectoris within the past 12 months prior to the first dose of the investigative product.
- Patient has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.
- Patient has history of malignancy within 5 years EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, *in situ* cervical cancer, or *in situ* breast ductal carcinoma.
- Patient has any concurrent medical condition that, in the opinion of the investigator, could cause this study to be detrimental to the patient.
- Patient has laboratory abnormalities at screening, including any of the following:
    - AST or ALT > 2x the upper limit of normal
    - serum direct bilirubin ~ 1.5 mg/dL
    - WBC count < 3.00 x 10^3/µL
    - ANC < 2.00 x 10^3/µL
    - any other laboratory abnormality, which, in the opinion of the investigator, will prevent the patient from completing the study or will interfere with the interpretation of the study results.
- Patient has known sensitivity to any of the products or components to be administered during dosing.
- For women (except if surgically sterile or at least 2 years postmenopausal, with postmenopausal status confirmed by FSH in the postmenopausal range): not willing to use highly effective methods of birth control during treatment and for 15 weeks after the last dose (if discontinuing before week 52) or for 8 weeks after the last dose (if discontinuing at or after week 52).
- For women: pregnant or breast feeding, or planning to become pregnant while enrolled in the study and for 15 weeks after the last dose (if discontinuing before week 52) or for 8 weeks after the last dose (if discontinuing at or after week 52).
- Patient will not be available for protocol required study visits or procedures, to the best of the patient's and investigator's knowledge.
- Patient has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the patient to give informed consent and/or to comply with all required study procedures.
- Patients receiving investigational procedures other than those listed in Table 5.

ANC, absolute neutrophil count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCG, Bacillus Calmette-Guerin; BSA, body surface area; FSH, follicle-stimulating hormone; PASI, Psoriasis Area and Severity Index; PPD, purified protein derivative; sPGA, static Physician's Global Assessment; WBC, white blood cell.
Source: Lebwohl *et al.* 2015, protocol (42); Papp *et al*. 2016 (41).

Table 5 Required drug washout period in the AMAGINE studies

Drug treatment or therapy	Washout period
Super-potent or potent topical steroids	28 days
Topical anthralin/dithranol	28 days
Other formulation or potency of topical therapy excepting upper mid-strength or lower potency topical steroids permitted on the face, axillae, and groin; bland emollients [without urea or alpha or beta hydroxy acids]; shampoo without steroids)	14 days
Ultraviolet A light therapy (with or without psoralen)	28 days
Ultraviolet B light therapy	28 days
Excimer laser	28 days
Oral retinoids	28 days
Methotrexate	28 days
Azathioprine	28 days
Cyclosporine	28 days
Systemically administered calcineurin inhibitors	28 days
Thioguanine	28 days
Hydroxyurea	28 days
Fumarates	28 days
Oral or parenteral corticosteroids including intramuscular or intraarticular administration	28 days
Other non-biological systemic therapy for psoriasis	28 days
Live vaccine	28 days [a]
Experimental or commercially available biological immune modulator(s) other than ustekinumab or anti-IL-17 biologics	12 weeks
Ustekinumab or anti-IL-17 therapy	Excluded

IL, interleukin.

[a] Or longer, according to local requirements for ustekinumab

Source: Lebwohl *et al.* 2015 (40).

B.2.3.1.4 Settings and locations

AMAGINE-2 and AMAGINE-3 were conducted at 142 sites in Australia, Canada, Europe, and the USA, with no overlap in study sites between the trials (40). AMAGINE-1 was conducted at 73 sites in Canada, Europe and the USA (41).

B.2.3.1.5 Outcomes

Outcome definitions were consistent across the AMAGINE trials, and are summarised in Table 6.

AMAGINE-2 and AMAGINE-3

Efficacy assessments were conducted throughout each study, with key assessments at week 12 (end of the induction phase) and week 52 (end of the maintenance phase). Disease activity was assessed at study visits with the Psoriasis Area Severity Index (PASI) and sPGA (40). In addition, nail involvement was assessed at baseline and week 12 with the Nail Psoriasis Severity Index (NAPSI) (42).

Patients performed symptom self-assessment with the PSI daily until week 24, then daily from week 48 to week 52. In addition, patients completed the DLQI at baseline and at weeks 2, 4, 8 and 12, then every 4 weeks until week 52 (42).

Both AMAGINE-2 and AMAGINE-3 tested three co-primary endpoints within two families of hypotheses, comparing brodalumab with placebo and brodalumab with ustekinumab (40). Primary endpoints, key secondary endpoints at week 12 and the maintenance endpoint at week 52 are listed in Table 7.

NICE clinical guideline 153 and the 2009 British Association of Dermatologists (BAD) guidelines use PASI 75 as a clinically meaningful endpoint that represents an adequate response to treatment (2, 29). However, the 2017 BAD guideline suggests that treatment targets may depend on clinical circumstances (56). The increased efficacy of more recent therapies for psoriasis suggests that for many patients with moderate-to-severe psoriasis PASI 100, representing complete clearing of psoriasis, may be the most appropriate endpoint (35).

Table 6 Outcome measures used in the AMAGINE trials

Outcome	Definition
Efficacy	
PASI score	The PASI score (0 to 72) is a measure of psoriasis disease severity based on a calculation of plaque qualities, including induration, erythema, and desquamation, and the area involved with psoriasis. The assessor scores plaque qualities (0 to 4) and area of involvement (0 to 6) for each of 4 body areas: head and neck, upper extremities, trunk, and lower extremities. Higher scores indicate more severe and/or extensive psoriasis (57).
PASI 100, PASI 90, PASI 75	Patients achieving 100% improvement (reduction) in PASI score compared with baseline are defined as PASI 100 responders (40). Other PASI thresholds reported in this submission are PASI 90 (≥ 90% improvement) and PASI 75 (≥ 75% improvement).
sPGA	The sPGA scale is designed to evaluate the assessor's global assessment of the subject's psoriasis based on severity of induration, scaling, and erythema. sPGA scores range from 0 (clear skin) to 5 (severe disease) (57).
NAPSI	NAPSI is an objective, numeric, and reproducible grading system which generates a score of 0 to 32 for each nail (58).
PSSI	The PSSI is a scalp-specific modification of the PASI, scored 0 to 72 based on the extent of involvement and the severity of erythema, induration, and desquamation (59).
Patient-reported outcomes	
PSI	The Psoriasis Symptom Inventory (PSI) is a validated patient-reported outcome measure for the assessment of plaque psoriasis symptoms, and consists of eight psoriasis-specific items addressing itch from psoriasis, and the redness, scaling, burning, cracking, stinging, flaking and pain of psoriasis lesions. Patients score the severity of symptoms in each item on a 5-point scale ranging from 0 (not at all severe) to 4 (very severe). Total scores range from 0 to 32, with higher scores indicating worse symptoms (60).
DLQI	The Dermatology Life Quality Index (DLQI) is a skin disease-specific instrument that has been validated for use in patients with psoriasis. The DLQI comprises ten questions based on skin disease symptoms and impact on HRQoL. DLQI scores range from 0 to 30, with higher scores indicating worse HRQoL (61). A 5-point improvement from baseline at a specific visit is defined as a clinically meaningful change (62), while a DLQI score of 0 or 1 indicates that the disease has no effect at all on a patient's life at a specific visit (63).

Outcome	Definition
HADS	HADS is a 14-item questionnaire to assess patients on seven items reflecting anxiety and seven reflecting depression. Each item is scored 0 to 3, for a total score from 0 to 21 for each of the anxiety and depression scales (64). For each scale, HADS severity groups are categorised as 'normal' (score 0–7), 'mild' (8–10), 'moderate' (11–14) and 'severe' (15–21).
EQ-5D	The EQ-5D is a standardised instrument developed by the EuroQoL Group for use as a generic, preference-based measure of health outcome. The EQ-5D questionnaire is used to calculate a utility score based on a descriptive profile, or 'health state'. Data in this submission, generated in AMAGINE-1, are based on the 3-level version (EQ-5D-3L), with UK preference weights.

DLQI, Dermatology Life Quality Index; EQ-5D, EuroQol-5D questionnaire; HADS, Hospital Anxiety and Depression Scale; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; PSSI, Psoriasis Scalp Severity Index; sPGA, static Physician's Global Assessment.

Table 7 Primary and key secondary endpoints in AMAGINE-2 and AMAGINE-3

Primary endpoints	
Comparison with placebo	• To evaluate the superiority of brodalumab (210 mg Q2W and 140 mg Q2W [a]) in patients with moderate-to-severe plaque psoriasis, as measured by the proportion of patients achieving 75% improvement in PASI score (PASI 75) at week 12 • To evaluate the superiority of brodalumab (210 mg Q2W and 140 mg Q2W [a]) in patients with moderate-to-severe plaque psoriasis, as measured by the proportion of patients achieving an sPGA response (clear [0] or almost clear [1]) at week 12
Comparison with ustekinumab	• To evaluate the superiority of brodalumab (210 mg Q2W; and weight-based analysis [b]) in clearing psoriasis in patients with moderate-to-severe plaque psoriasis, measured by the proportion of patients achieving PASI 100 at week 12
Key secondary endpoints	
Comparison with placebo	• To evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W a) in clearing psoriasis, as measured by the proportion of patients achieving PASI 100 at week 12 • To evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W a) in clearing psoriasis, as measured by the proportion of patients achieving an sPGA score of 0 (clear) at week 12 • To evaluate the effect of brodalumab (210 mg Q2W and 140 mg Q2W a) on patient-reported symptoms of psoriasis, as measured by the proportion of patients who meet the responder definition for the PSI (total score ≤ 8, with no item scores > 1) at week 12
Comparison with ustekinumab	• To evaluate the efficacy of brodalumab (140 mg Q2W a) in clearing psoriasis, as measured by the proportion of patients achieving PASI 100 at week 12 • To evaluate the efficacy of brodalumab (210 mg Q2W; and weight-based analysis b), as measured by the proportion of patients achieving PASI 75 at week 12
Maintenance endpoint	
Comparison with ustekinumab	• To compare the efficacy of brodalumab maintenance regimens, as measured by the proportion of patients achieving an sPGA response (clear [0] or almost clear [1]) at week 52

a Brodalumab 140 mg Q2W is outside the proposed label for brodalumab in the treatment of moderate-to-severe plaque psoriasis; these results are not described in detail in this submission, but are summarised in Appendix L and published in Lebwohl *et al.* 2015 (40).
b The weight-based analysis group was a pre-specified subgroup that included patients with a body weight of ≤ 100 kg in the 140 mg Q2W group and of > 100 kg in the 210 mg Q2W group. Weight-based dosing is outside the proposed label for brodalumab in the treatment of moderate-to-severe plaque psoriasis, and these results are not described in detail in this submission.
PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; Q2W, every 2 weeks; sPGA, static Physician's Global Assessment. Source: Lebwohl *et al.* 2015 (40); Lebwohl *et al.* 2015, protocol (42)

AMAGINE-1

Efficacy assessments were conducted throughout each study, with key assessments at week 12 (end of the induction phase) and week 52 (end of the maintenance phase). Disease activity was assessed at study visits with the PASI and sPGA (41). Psoriasis Scalp Severity Index (PSSI) assessments, which were not conducted in AMAGINE-2 and AMAGINE-3, were included at baseline and week 12 in AMAGINE-1.

Patients performed symptom self-assessment with the PSI daily until week 24, then daily from week 48 to week 52. In addition, patients completed the DLQI at baseline and at weeks 2, 4, 8 and 12, then every 4 weeks until week 52, and the EuroQol-5D questionnaire (EQ-5D) at baseline and at weeks 4, 8 and 12 (41, 48). AMAGINE-1 also included the Hospital Anxiety and Depression Scale (HADS), which was completed at baseline and at weeks 12, 24, 36 and 52 (41, 48).

Primary and key second endpoints in AMAGINE-1 are summarised in Table 8 (41).

Table 8 Primary and key secondary endpoints in AMAGINE-1

Primary endpoints
• To evaluate the superiority of brodalumab (210 mg Q2W and 140 mg Q2W [a]) in patients with moderate-to-severe plaque psoriasis, as measured by the proportion of patients achieving 75% improvement in PASI score (PASI 75) at week 12 • To evaluate the superiority of brodalumab (210 mg Q2W and 140 mg Q2W [a]) in patients with moderate-to-severe plaque psoriasis, as measured by the proportion of patients achieving an sPGA response (clear [0] or almost clear [1]) [b] at week 12
Key secondary endpoints
• To evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W [a]) in clearing psoriasis, as measured by the proportion of patients achieving PASI 100 at week 12 • To evaluate the efficacy of brodalumab (210 mg Q2W and 140 mg Q2W [a]) in clearing psoriasis, as measured by the proportion of patients achieving an sPGA score of 0 at week 12 • To evaluate the effect of brodalumab (210 mg Q2W and 140 mg Q2W [a]) on patient-reported symptoms of psoriasis, as measured by the proportion of patients who meet the responder definition for the PSI (total score ≤ 8, with no item scores > 1) at week 12 • To compare the efficacy of brodalumab maintenance regimens, as measured by the proportion of patients achieving an sPGA response (clear [0] or almost clear [1]) at week 52

[a] Brodalumab 140 mg Q2W is outside the proposed label for brodalumab in the treatment of moderate-to-severe plaque psoriasis; these results are not described in detail in this submission, but are summarised in Appendix L and published in Papp *et al*. 2016 (41).
[b] sPGA response (clear [0] or almost clear [1]) was referred to as 'sPGA success' in Papp *et al*. 2016 (41).
PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; Q2W, every 2 weeks; sPGA, static Physician's Global Assessment. Source: Papp *et al*. 2016 (41).

B.2.3.2 Summary table

A comparative summary of the methodology of the AMAGINE trials is shown in Table 9.

B.2.3.3 Baseline characteristics

Demographics and baseline characteristics of patients included in the three AMAGINE studies are shown in Table 10. In all three studies, baseline characteristics were balanced across the treatment groups (40, 41).

Table 9 Comparative summary of trial methodology

Trial number (acronym)	NCT01708603 (AMAGINE-2) and NCT01708629 (AMAGINE-3) (40, 42-44)	NCT01708590 (AMAGINE-1) (41, 45, 48)
Location	Both trials were conducted at 142 sites in Australia, Canada, Europe, and the USA, with no overlap in study sites between the trials	73 sites in Canada, Europe and the USA
Trial design	Multicentre, randomised, double-blind, placebo- and active comparator-controlled, parallel-group phase 3 trials, comprising: a) 12-week induction phase b) 40-week maintenance phase c) Open-label long-term extension phase (weeks 52–120 [AMAGINE-2] or weeks 52–108 [AMAGINE-3])	Multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trial, comprising: a) 12-week induction phase b) 40-week withdrawal and re-treatment phase c) Open-label long-term extension phase (weeks 52–120)
Eligibility criteria for participants	Adults aged 18 to 75 years who were candidates for biological therapy for stable moderate-to-severe plaque psoriasis of at least 6 months' duration and who had a PASI score of 12 or higher, an sPGA score of 3 or higher, and involvement of 10% or more of the body surface area. Full inclusion and exclusion criteria are listed in Table 4.	Adults aged 18 to 75 years who were candidates for biological therapy for stable moderate-to-severe plaque psoriasis of at least 6 months' duration and who had a PASI score of 12 or higher, an sPGA score of 3 or higher, and involvement of 10% or more of the body surface area. Full inclusion and exclusion criteria are listed in Table 4.
Settings and locations where the data were collected	Data were collected during scheduled visits to study centres.	Data were collected during scheduled visits to study centres.
Trial drugs **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	**Induction phase** 2:2:1:1 ratio of brodalumab 210 mg Q2W, brodalumab 140 mg Q2W, placebo (all day 1 and weeks 1, 2, 4, 6, 8, and 10) or ustekinumab (day 1, week 4 and then Q12W) *AMAGINE-2:* brodalumab 210 mg Q2W, n = 612; brodalumab 140 mg Q2W, n = 610; placebo, n = 309; ustekinumab, n = 300	**Induction phase** 1:1:1 ratio of brodalumab 210 mg Q2W, brodalumab 140 mg Q2W or placebo (all day 1 and weeks 1, 2, 4, 6, 8, and 10) Brodalumab 210 mg Q2W, n = 222; brodalumab 140 mg Q2W, n = 219; placebo, n = 220

Trial number (acronym)	NCT01708603 (AMAGINE-2) and NCT01708629 (AMAGINE-3) (40, 42-44)	NCT01708590 (AMAGINE-1) (41, 45, 48)
	AMAGINE-3: brodalumab 210 mg Q2W, n = 624; brodalumab 140 mg Q2W, n = 629; placebo, n = 315; ustekinumab, n = 313 **Maintenance phase** Patients randomised to brodalumab were re-randomised 2:2:2:1 to brodalumab 210 mg Q2W, brodalumab 140 mg Q2W, brodalumab 140 mg Q4W or brodalumab 140 mg Q8W Patients randomised to ustekinumab: continued to receive ustekinumab Patients randomised to placebo: brodalumab 210 mg Q2W Patients with inadequate response received rescue treatment: brodalumab groups received brodalumab 210 mg Q2W rescue treatment; ustekinumab group received ustekinumab rescue treatment, except for those with an inadequate response at week 16, who switched to brodalumab 210 mg Q2W *AMAGINE-2:* brodalumab 210 mg Q2W, n = 334; brodalumab 140 mg Q2W, n =337; brodalumab 140 mg Q4W, n = 335; brodalumab 140 mg Q8W, n = 168; ustekinumab, n = 289; placebo then brodalumab 210 mg Q2W, n = 297 *AMAGINE-3:* brodalumab 210 mg Q2W, n = 342; brodalumab 140 mg Q2W, n =343; brodalumab 140 mg Q4W, n = 341; brodalumab 140 mg Q8W, n = 174; ustekinumab, n = 301; placebo then brodalumab 210 mg Q2W, n = 298 Details of rescue therapy are shown in section B.2.6.2.3. Before week 28, investigational product was administered by a qualified staff member. Starting at week 28, patients were permitted to self-administer investigational product every other week by subcutaneous injection Investigators could prescribe any concomitant medications or	**Withdrawal and re-treatment phase** Patients randomised to brodalumab who had an sPGA response (clear [0] or almost clear [1]) were re-randomised 1:1 to their induction dose of brodalumab or placebo. All other patients received brodalumab 210 mg Q2W. Patients in the withdrawal phase who experienced return of disease (sPGA ≥ 3) between weeks 16 and 52 were re-treated with their induction dose of brodalumab (41). Initial brodalumab 210 mg group with an sPGA response (n = 167): brodalumab 210 mg Q2W, n = 83; placebo, n = 84 Initial brodalumab 210 mg group with sPGA ≥ 3: brodalumab 210 mg Q2W, n = 45 Initial brodalumab 140 mg group with an sPGA response (n = 116): brodalumab 140 mg Q2W, n = 57; placebo, n = 59 Initial brodalumab 140 mg group with sPGA ≥ 3: brodalumab 210 mg Q2W, n = 52 Initial placebo group: brodalumab 210 mg Q2W, n = 208 Details of re-treatment are shown in B.2.6.3.2. Before week 24, investigational product was administered by a qualified staff member. Starting at week 24, patients were permitted to self-administer investigational product every other week by subcutaneous injection Investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for psoriasis therapies,

Trial number (acronym)	NCT01708603 (AMAGINE-2) and NCT01708629 (AMAGINE-3) (40, 42-44)	NCT01708590 (AMAGINE-1) (41, 45, 48)
	treatments deemed necessary to provide adequate supportive care except for psoriasis therapies, for which washout periods were required as shown in Table 5.	for which washout periods were required as shown in Table 5.
Primary outcomes (including scoring methods and timings of assessments)	• Proportion of patients with 100% improvement in PASI score (PASI 100; see section B.2.3.1.5) at week 12 • Proportion of patients with 75% improvement in PASI score (PASI 75) at week 12 • Proportion of patients achieving an sPGA response (clear [0] or almost clear [1]) at week 12	• Proportion of patients with 75% improvement in PASI score (PASI 75) at week 12 • Proportion of patients achieving an sPGA response (clear [0] or almost clear [1]) at week 12
Other outcomes used in the economic model/specified in the scope	• Nail involvement was assessed using the NAPSI (see section B.2.3.1.5) • HRQoL, measured as the proportion of patients with a 5-point improvement in DLQI score, and the proportion with DLQI scores of 0 or 1 (see section B.2.3.1.5)	• Scalp psoriasis was assessed using the PSSI (see section B.2.3.1.5) • HRQoL, measured as the proportion of patients with a 5-point improvement in DLQI score, and the proportion with DLQI scores of 0 or 1 (see section B.2.3.1.5) • HRQoL, measured with the HADS questionnaire (see section B.2.3.1.5) • Utility values, measured with the EQ-5D, are used in the cost-effectiveness model described in section B3
Pre-planned subgroups	• Severity of psoriasis (PASI < 20 or ≥ 20) • Prior use of systemic or photo therapies (yes or no) • Systemic agent failure or contraindication (yes or no) • Prior use of biological therapy (yes or no) • Previous failure of biological therapy (yes or no) • Previous use of anti-TNF therapy (yes or no)	

DLQI, Dermatology Life Quality Index; EQ-5D, EuroQol-5D questionnaire; HADS, Hospital Anxiety and Depression Scale; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; PSSI, Psoriasis Scalp Severity Index; sPGA, static Physician's Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks.

Table 10 Demographics and baseline clinical characteristics of patients in the AMAGINE studies (FAS)

	AMAGINE-2			AMAGINE-3			AMAGINE-1	
	Placebo (N = 309)	Ustekinumab (N = 300)	Brodalumab 210 mg Q2W (N = 612)	Placebo (N = 315)	Ustekinumab (N = 313)	Brodalumab 210 mg Q2W (N = 624)	Placebo (N = 220)	Brodalumab 210 mg Q2W (N = 222)
Mean age, years ± SD	44 ± 13	45 ± 13	45 ± 13	44 ± 13	45 ± 13	45 ± 13	47 ± 13	46 ± 12
Sex, n (%) men	219 (71)	205 (68)	421 (69)	208 (66)	212 (68)	431 (69)	161 (73)	161 (73)
Race, n (%) white [a]	273 (88)	271 (90)	551 (90)	294 (93)	280 (90)	565 (91)	202 (92)	203 (91)
Mean weight, kg ± SD	92 ± 23	91 ± 24	91 ± 23	89 ± 22	90 ± 22	90 ± 23	90.4 ± 20.1	91.4 ± 23.4
Mean body mass index ± SD [b]	30.5 ± 7.0	30.6 ± 7.1	30.5 ± 7.2	29.9 ± 6.7	30.4 ± 6.8	30.3 ± 7.3	30.3 ± 6.6	31.0 ± 7.7
Mean duration of psoriasis, years ± SD	18 ± 12	19 ± 13	19 ± 12	18 ± 12	18 ± 12	18 ± 12	21 ± 12	20 ± 13
Psoriatic arthritis, n (%)	51 (17)	50 (17)	114 (19)	59 (19)	64 (20)	127 (20)	63 (29)	58 (26)
Mean body surface area involved, % ± SD	28 ± 17	27 ± 19	26 ± 16	28 ± 17	28 ± 18	28 ± 18	26.9 ± 17.1	25.1 ± 15.3
Mean PASI score ± SD [c]	20.4 ± 8.2	20.0 ± 8.4	20.3 ± 8.3	20.1 ± 8.7	20.1 ± 8.4	20.4 ± 8.3	19.7 ± 7.7	19.4 ± 6.6
sPGA — n (%) [d]								
3 (moderate disease)	167 (54)	153 (51)	316 (52)	192 (61)	192 (61)	373 (60)	114 (52)	121 (55)
4	120 (39)	132 (44)	254 (42)	113 (36)	103 (33)	226 (36)	91 (41)	87 (39)
5 (very severe)	22 (7)	15 (5)	42 (7)	10 (3)	18 (6)	25 (4)	15 (7)	14 (6)
Mean PSI score ± SD [e]	18.6 ± 7.1	18.9 ± 7.0	18.6 ± 6.8	19.0 ± 6.7	18.7 ± 6.8	18.7 ± 7.2	19.0 ± 6.7	18.9 ± 6.7
Mean DLQI score ± SD [f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13.9 ± 6.8	14.2 ± 7.3
Previous systemic treatment or phototherapy, n (%)	230 (74)	225 (75)	469 (77)	206 (65)	220 (70)	422 (68)	182 (83)	179 (81)
Previous biological therapy, n (%)	90 (29)	84 (28)	177 (29)	76 (24)	75 (24)	157 (25)	101 (46)	105 (47)

[a] Race was self-reported.
[b] The body mass index is the weight in kilograms divided by the square of the height in metres.
[c] PASI scores range from 0 to 72, with higher scores indicating more severe disease.
[d] sPGA scores range from 0 (clear) to 5 (very severe); a score of 3 indicates moderate disease.
[e] PSI scores range from 0 to 32, with higher scores indicating more severe disease.
[f] DLQI scores range from 0 to 30, with higher scores indicating worse HRQoL.
DLQI, Dermatology Life Quality Index; FAS, full analysis set; HRQoL, health-related quality of life; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; SD, standard deviation; sPGA, static physician global assessment; Q2W, every 2 weeks.
Source: Lebwohl *et al.* 2015 (40); Papp *et al.* (2016) (41); AMAGINE-1 CSR (44); AMAGINE-2 CSR (43); AMAGINE-3 CSR (44).

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

B.2.4.1 Sample size calculation and testing procedure

AMAGINE-2 and AMAGINE-3

A sample size calculation was conducted using a logistic regression model adjusted by total body weight group. With alpha = 0.01 (2-sided), sample sizes of 600 patients for each of the brodalumab groups (210 mg Q2W and 140 mg Q2W) and 300 patients for the placebo group were calculated to provide more than 90% power to detect the difference in all the comparisons within the placebo family of co-primary and key secondary endpoints. Similarly, a total of 600 patients for each of the brodalumab groups and 300 patients for the ustekinumab group was calculated provide more than 90% power to detect the difference in all the PASI 75 and PASI 100 comparisons within the ustekinumab family of primary and key secondary endpoints (alpha = 0.04) (40).

For the maintenance endpoint, the total sample size of 1800 patients was calculated to provide more than 90% power to detect a difference in sPGA response between brodalumab groups at week 52, assuming a 15% dropout rate at week 12 (40).

The multiple testing procedure employed to test the two families of hypotheses maintained an overall family-wise type-1 error rate at 5%, and the sample size provided marginal power of 90% or more for each pair of null and alternative hypotheses (40).

AMAGINE-1

Using a Cochran-Mantel-Haenszel model stratified by total bodyweight group, it was computed that 200 patients per arm (600 total) would provide > 90% power to detect a difference between either dose of brodalumab (140 or 210 mg Q2W) and the placebo group in both the sPGA and PASI 75 response rate. For the randomised withdrawal phase, it was assumed that 77% and 72% of patients initially randomised to the 210 mg and 140 mg doses of brodalumab, respectively, would be re-randomised at week 12. Assuming that the sPGA response rate at week 52 for both brodalumab groups would be 65% and for the withdrawal groups would be 35, the power to detect a difference between the proportion of responders at week 52 was computed to be ≥ 90% for both doses of brodalumab, at an alpha = 0.05 two-sided level.

B.2.4.2 Analysis populations

Primary analyses were conducted after all patients for each study completed the week 52 visit or terminated the study. Efficacy analyses for the primary endpoint at week 12 were conducted using the full analysis set (FAS), which includes all patients randomised to treatment regardless of the actual treatment received during the study (40, 41).

In AMAGINE-2 and AMAGINE-3, analysis of the maintenance endpoint (sPGA response at week 52) was conducted using the efficacy analysis set (EAS), which included only those patients who were re-randomised at week 12 (42). In AMAGINE-1, analysis of the maintenance endpoint (sPGA response at week 52) was based on patients who had an sPGA response at week 12 and were re-randomised to brodalumab; patients with an sPGA response at week 12 who were re-randomised to placebo were included in the withdrawal and re-treatment analysis (41).

In each study, the safety analysis set included all randomised patients who received one or more doses of investigational product (40). Efficacy analyses for the open-label long-term extension phase were conducted for all patients who entered the extension phase at week 52 (49, 50).

B.2.4.3 Statistical methods

AMAGINE-2 and AMAGINE-3

The efficacy analyses in AMAGINE-2 and AMAGINE-3 consisted of two families of primary and key secondary endpoints, comparing brodalumab with placebo and with ustekinumab. For 12-week endpoints, the testing approach used a combination of parallel, sequential, and Bonferroni-based recycling testing (primary followed by key secondary endpoints) to maintain an overall 2-sided family-wise type-1 error rate at 5%. Initial testing was based on a two-sided alpha of 0.01 in the placebo family, and 0.04 in the ustekinumab family – after null hypotheses in the placebo family were rejected, the ustekinumab hypotheses were tested at alpha = 0.05. The maintenance endpoint at week 52 was tested separately from the week 12 analysis testing, at alpha = 0.05. *p* values for primary and key secondary endpoints were adjusted for multiplicity; all other *p* values are nominal (40). The order in which endpoints were tested within each family of hypotheses is shown in Table 11. If the results for an endpoint were not significantly different between groups, subsequent endpoints were not formally tested for statistical significance (40, 42).

Table 11 Order of hypothesis testing in AMAGINE-2 and AMAGINE-3

	Placebo family, 12 weeks	Ustekinumab family, 12 weeks
Primary endpoints	PASI 75: 210 mg Q2W sPGA response: 210 mg Q2W PASI 75: 140 mg Q2W [b] sPGA response: 140 mg Q2W [b]	PASI 100: 210 mg Q2W PASI 100: weight-based [a]
Secondary endpoints	PASI 75: 210 mg Q2W sPGA of 0: 210 mg Q2W PASI 100: 140 mg Q2W [b] sPGA of 0: 140 mg Q2W [b] PSI responder: 210 mg Q2W PSI responder: 140 mg Q2W [b]	PASI 100: 140 mg Q2W [b] PASI 75: 210 mg Q2W PASI 75: weight-based [a]

a The weight-based analysis group was a pre-specified subgroup that included patients with a body weight of ≤ 100 kg in the 140 mg Q2W group and of > 100 kg in the 210 mg Q2W group. Weight-based dosing is outside the proposed label for brodalumab in the treatment of moderate-to-severe plaque psoriasis, and these results are not described in detail in this submission.
b Brodalumab 140 mg Q2W is outside the proposed label for brodalumab in the treatment of moderate-to-severe plaque psoriasis, and these results are not described in detail in this submission.
Source: Lebwohl *et al.* 2015, protocol (42).

AMAGINE-1

In AMAGINE-1, *p* values were adjusted for multiplicity using a sequential testing procedure, with the co-primary end points tested simultaneously at the 0.05 alpha level. If both primary endpoints were significant, key secondary end points were tested sequentially. The *p* values for all other end points were not adjusted for multiplicity (41).

No hypothesis testing was performed for the open-label long-term extension phase (45, 49, 50).

B.2.4.4 Imputation

For 12-week analyses of PASI, sPGA, PSI and PSSI (AMAGINE-1 only) response rates, missing data were imputed by non-responder imputation (NRI) for dichotomous endpoints (40, 41). NRI is considered to be a more conservative approach for managing missing data than last observation carried forward (LOCF) (65). The 12-week NAPSI score analysis (AMAGINE-2 and AMAGINE-3) was conducted using multiple imputation (43, 44).

After week 12 in AMAGINE-2 and AMAGINE-3, analyses for patients receiving placebo or ustekinumab during the induction phase and initiating brodalumab 210 mg Q2W at weeks 12 or 16, respectively, were as observed, with no imputation (42). During the AMAGINE-1 withdrawal phase, responses in patients with return of disease and re-treatment were as observed, with no imputation (41).

For analyses of all other patients during the maintenance phase, missing values for dichotomous endpoints were imputed by NRI, unless otherwise specified; continuous variables were imputed using LOCF. For testing the maintenance phase endpoint (sPGA response at week 52), patients who had an inadequate response (defined as a single sPGA of ≥ 3 or persistent sPGA values of 2 over at least a 4-week period) during the maintenance phase were categorised as non-responders (NRI after inadequate response) (40, 41).

Open-label long-term extension phase analyses were conducted using as observed data, with no imputation.

B.2.4.5 Participant flow

Full details of patient disposition in the three AMAGINE studies are shown in Appendix D. In AMAGINE-2, 1,831 patients underwent randomisation, 1,776 (97%) completed the 12-week induction phase, and 1,601 (87%) completed the 52-week maintenance phase. In AMAGINE-3, 1,881 patients were randomised, 1,816 (97%) completed the 12-week induction phase, and 1,656 (88%) completed the 52-week maintenance phase (40).

In AMAGINE-2, 55 of 300 patients (18%) assigned to receive ustekinumab were given rescue therapy with brodalumab at week 16; 69 of 313 patients (22%) in the AMAGINE-3 ustekinumab group received brodalumab rescue therapy.

In AMAGINE-1, 661 patients were randomised, and 633 completed the induction phase. Among the 84 patients with an initial sPGA response on brodalumab 210 mg Q2W who were re-randomised to placebo at week 12, 79 experienced a return of disease (sPGA ≥ 3) during the withdrawal phase and were re-treated with brodalumab 210 mg Q2W.

Across all three studies, the main reasons for discontinuation were withdrawal of consent (AMAGINE-1, n = 10; AMAGINE-2, n = 82; AMAGINE-3, n = 86), adverse events (AMAGINE-1, n = 8; AMAGINE-2, n = 40; AMAGINE-3, n = 31) and loss to follow-up (AMAGINE-1, n = 3; AMAGINE-2, n = 19; AMAGINE-3, n = 28) (40). No patient treated with brodalumab 210 mg Q2W or ustekinumab discontinued the study due to lack of response (in each of AMAGINE-2 and AMAGINE-3 3 patients initially randomised to placebo discontinued due to lack of response) (43, 44).

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A summary of the quality assessment for the AMAGINE trials is shown in Table 12, with a detailed description of the quality assessment presented in Appendix D, Table 86. The three RCTs were of high quality, and had a low risk of bias. Baseline characteristics were balanced across randomised groups, and blinding was maintained throughout.

The main outcome measure in the AMAGINE trials is improvement in PASI score, which is used in NICE guidance and BAD guidelines as a measure of treatment success in psoriasis (2, 29). In addition, the AMAGINE studies were designed to include a typical moderate-severe psoriasis population with few restrictions - baseline characteristics in the trial were similar to those of the BADBIR population (see section B.2.13) (66). Consequently, the AMAGINE trials are likely to reflect clinical practice in England.

Table 12 Quality assessment results for AMAGINE trials

Trial number (acronym)	NCT01708590 (AMAGINE-1)	NCT01708603 (AMAGINE-2)	NCT01708629 (AMAGINE-3)
Was randomisation carried out appropriately?	YES	YES	YES
Was the concealment of treatment allocation adequate?	YES	YES	YES
Were the groups similar at the outset of the study in terms of prognostic factors?	YES	YES	YES
Were the care providers, participants and outcome assessors blind to treatment allocation?	YES	YES	YES
Were there any unexpected imbalances in drop-outs between groups?	NO	NO	NO
Is there any evidence to suggest that the authors measured more outcomes than they reported?	NO	NO	NO
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	YES	YES	YES

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).
Sources: Lebwohl *et al.* 2015 (40); Papp *et al.* 2016 (41); AMAGINE-1, AMAGINE-2 and AMAGINE-3 CSRs (43, 44, 48).

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Summary of key efficacy endpoint results at week 12

Results for the key efficacy endpoints in AMAGINE-2, AMAGINE-3 and AMAGINE-1 are summarised in Table 13. All three trials met their primary endpoints, and all primary and key secondary endpoints in the placebo family of comparisons showed significantly greater efficacy with brodalumab than with placebo (40, 41).

In AMAGINE-2 and AMAGINE-3, testing of the primary endpoint in the ustekinumab family of comparisons found significantly higher PASI 100 response rates with brodalumab 210 mg Q2W than with ustekinumab (see section B.2.6.2.2). In AMAGINE-2, 44% (95% confidence interval [CI], 41–49%) of patients receiving brodalumab 210 mg Q2W achieved PASI 100 at week 12, compared

with 22% (95% CI, 17–27%) in the ustekinumab group ($p < 0.001$); in AMAGINE-3, the corresponding PASI 100 response rates were 37% (95% CI, 33–41%) with brodalumab 210 mg Q2W and 19% (95% CI, 14–23%) with ustekinumab ($p < 0.001$) (40).

PASI 75 response rates were 86% and 85% with brodalumab 210 mg Q2W in AMAGINE-2 and AMAGINE-3, respectively, significantly higher than with placebo (8% and 6%; $p < 0.001$; see section B.2.6.2.2). In addition, the proportion of patients with sPGA scores of clear (0) or almost clear (1) was significantly higher with brodalumab 210 mg Q2W than with placebo (79% and 80% vs 4% and 4%; $p < 0.001$) (40).

In AMAGINE-3, response rates for all key secondary endpoints including PASI 75 response were significantly higher with brodalumab 210 mg Q2W than with ustekinumab (Table 13). In AMAGINE-2, the result of the PASI 75 endpoint for brodalumab 210 mg Q2W versus ustekinumab favoured brodalumab (86% vs 70%; nominal $p < 0.001$; see section B.2.4.3.1 for description of formal testing procedure) (40).

In AMAGINE-1, the PASI 75 response rate at week 12 was 83% with brodalumab 210 mg Q2W, compared with 3% with placebo ($p < 0.001$). In total, 93 of 222 patients treated with brodalumab 210 mg Q2W (42%) had clear skin (PASI 100, sPGA 0) at week 12, compared with 1 of 220 patients in the placebo group (0.5%; $p < 0.001$).

B.2.6.2 AMAGINE-2 and AMAGINE-3

B.2.6.2.1 Statistical significance of primary and key secondary endpoints

In both AMAGINE-2 and AMAGINE-3, all primary and key secondary endpoints in the placebo family of hypotheses showed statistically significantly greater efficacy with brodalumab than with placebo, at a significance level of 0.01 (Table 13). Primary and key secondary endpoints in the ustekinumab family of hypotheses were therefore tested at a significance level of 0.05, in the predefined order (see section B.2.4.3) (40).

Brodalumab demonstrated significantly greater efficacy than ustekinumab with regard to the primary endpoints in both studies, as well as with regard to all key secondary endpoints in AMAGINE-3 (Table 14) (40).The nominal p value for PASI 75 response with the 210 mg Q2W dose of brodalumab, which is the approved dose described in this submission, was significant ($p < 0.001$) (40).

Table 13 Clinical responses and patient-reported outcomes at week 12 in the AMAGINE trials (FAS, NRI)

Outcome	AMAGINE-2			AMAGINE-3			AMAGINE-1	
	Placebo (N = 309)	Ustekinumab (N = 300)	Brodalumab 210 mg Q2W (N = 612)	Placebo (N = 315)	Ustekinumab (N = 313)	Brodalumab 210 mg Q2W (N = 624)	Placebo (N = 220)	Brodalumab 210 mg Q2W (N = 222)
PASI 100, n	2	65	272	1	58	229	1	93
% (95% CI)	1 (0–2)	22 (17–27)	44 (41–49)	0.3 (0–2)	19 (14–23)	37 (33–41)	0.5 (0–3)	42 (35–49)
p value vs placebo [a]	—	—	< 0.001	—	—	< 0.001	—	< 0.001
p value vs ustekinumab [a]	—	—	**< 0.001** [b]	—	—	**< 0.001** [b]	—	—
PASI 75, n	25	210	528	19	217	531	6	185
% (95% CI)	8 (5–12)	70 (65–75)	86 (83–89)	6 (4–9)	69 (64–74)	85 (82–88)	3 (1–6)	83 (78–88)
p value vs placebo [a,c]	—	—	**< 0.001**	—	—	**< 0.001**	—	**< 0.001** [c]
p value vs ustekinumab	—	—	NT [a]	—	—	0.007 [a]	—	—
sPGA score of 0 or 1, n	12	183	481	13	179	497	3	168
% (95% CI)	4 (2–7)	61 (55–67)	79 (75–82)	4 (2–7)	57 (52–63)	80 (76–83)	1 (0–4)	76 (70–81)
p value vs placebo [a,c]	—	—	**< 0.001**	—	—	**< 0.001**	—	**< 0.001** [c]
p value vs ustekinumab	—	—	< 0.001	—	—	< 0.001	—	—
sPGA score of 0, n	2	65	274	1	58	229	1	93
% (95% CI)	1 (0–2)	22 (17–27)	45 (41–49)	0.3 (0–2)	19 (14–23)	37 (33–41)	0.5 (0–3)	42 (35–49)
p value vs placebo [a]	—	—	< 0.001	—	—	< 0.001	—	< 0.001
p value vs ustekinumab	—	—	< 0.001	—	—	< 0.001	—	—
PSI response, n [d]	21	166	414	20	162	382	9	135
% (95% CI)	7 (4–10)	55 (50–61)	68 (64–71)	6 (4–10)	52 (46–57)	61 (57–65)	4 (2–8)	61 (54–67)
p value vs placebo [a]	—	—	< 0.001	—	—	< 0.001	—	< 0.001
p value vs ustekinumab	—	—	< 0.001	—	—	< 0.001	—	—

Missing data were imputed as nonresponses (see section B.2.4.4). *p* values for primary endpoints are shown in bold.
PASI 75 and PASI 100 responses indicate reductions from baseline in the PASI score of 75% or more and 100%, respectively. N values are the numbers of patients who were randomly assigned to a study regimen and had a valid measurement value at week 12, after imputation. All *p* values were nominal except as noted otherwise. *p* values were not calculated for the comparison of brodalumab and ustekinumab for the PSI response definition.
[a] *p* values were calculated by means of Bonferroni-based recycling testing (see section B.2.4.3), which includes all primary and key secondary end point comparisons with placebo and ustekinumab, at a significance level of 0.05.
[b] The *p* value is for the primary end point in the comparison of brodalumab with ustekinumab.
[c] *p* values in this row are for the co-primary endpoints in the comparison of brodalumab with placebo.
[d] A PSI response was defined as a total score of up to 8, with no item having a score greater than 1.
FAS, full analysis set; NRI, non-responder imputation; NT, not tested; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: Lebwohl *et al*. 2015 (42); Papp *et al.* 2016 (41); AMAGINE-1 CSR (48).

Table 14 Statistical significance of comparisons between brodalumab and ustekinumab in AMAGINE-2 and AMAGINE-3 (FAS, NRI)

Comparison – brodalumab vs ustekinumab at week 12	AMAGINE-2		AMAGINE-3	
	Nominal *p* value	Adjusted *p* value	Nominal *p* value	Adjusted *p* value
Primary endpoints				
PASI 100: 210 mg Q2W	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
PASI 100: weight-based [a]	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Key secondary endpoints				
PASI 100: 140 mg Q2W [b]	0.078	0.078 [c]	**0.007**	**0.007**
PASI 75: 210 mg Q2W	**< 0.001**	NT [c]	**< 0.001**	**0.007**
PASI 75: weight-based [a]	[redacted]	NT [c]	**0.007**	**0.007**

Statistically significant p values are shown in bold.
[a] The weight-based analysis group was a pre-specified subgroup that included patients with a body weight of ≤ 100 kg in the 140 mg Q2W group and of > 100 kg in the 210 mg Q2W group. Weight-based dosing is outside the proposed label for brodalumab in the treatment of moderate-to-severe plaque psoriasis, and these results are not described in detail in this submission.
[b] Brodalumab 140 mg Q2W is outside the proposed label for brodalumab in the treatment of moderate-to-severe plaque psoriasis, and these results are not described in detail in this submission.
[c] In AMAGINE-2, the increase in PASI 100 response rate with brodalumab 140 mg Q2W versus ustekinumab was not statistically significant, and subsequent hypotheses were not formally tested.
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; Q2W, every 2 weeks
Source: Lebwohl *et al.* 2015 (42); AMAGINE-2 CSR (43); AMAGINE-3 CSR (44).

B.2.6.2.2 Clinical responses during induction phase

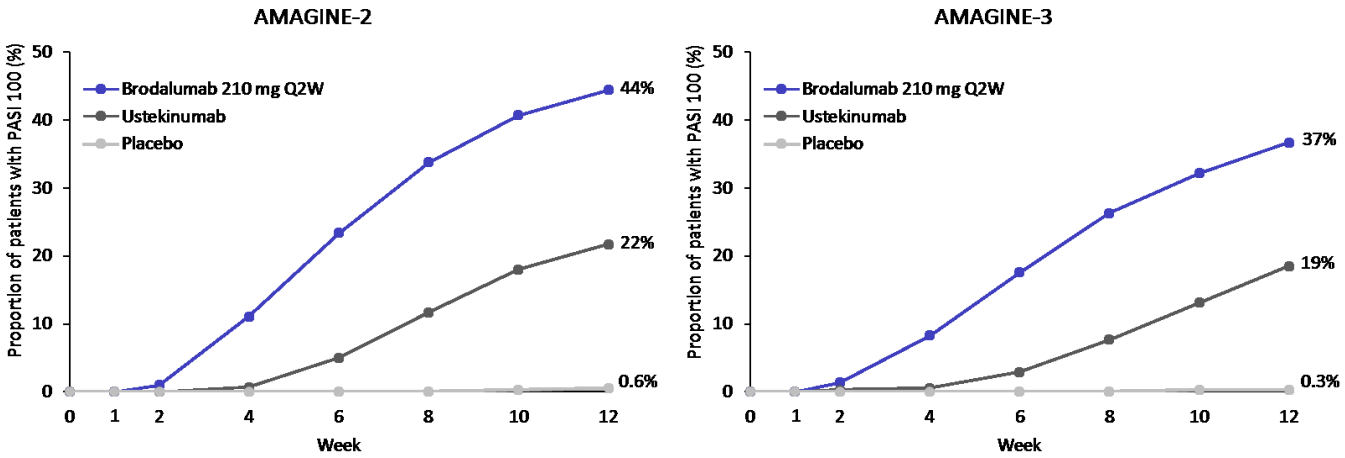
PASI 100 response (primary endpoint vs ustekinumab)

Almost twice as many patients achieved PASI 100 with brodalumab than with ustekinumab
The proportion of patients achieving 100% improvement in PASI score (PASI 100) at week 12 was a co-primary endpoint for the comparison of brodalumab with ustekinumab. In AMAGINE-2, 44.4% (95% CI, 40.5–48.5%) of patients in the brodalumab 210 mg Q2W group achieved PASI 100 at week 12, compared with 21.7% (17.1–26.8%) of those in the ustekinumab group ($p < 0.001$). Similarly, in AMAGINE-3, PASI 100 was achieved by 36.7% (32.9–40.6%) of patients receiving brodalumab 210 mg Q2W and 18.5% (14.4–23.3%) of those receiving ustekinumab ($p < 0.001$) (40).

As early as week 4, PASI 100 responses were achieved by significantly more patients with brodalumab than with ustekinumab
The response to brodalumab 210 mg Q2W was more rapid than that to ustekinumab (Figure 6), with a significant difference seen as early as week 4: [redacted] receiving brodalumab 210 mg Q2W in AMAGINE-2 and [redacted] in AMAGINE-3 achieved PASI 100 at week 4, compared with [redacted] and [redacted] in the respective ustekinumab groups (both [redacted]) (43, 44).

In the AMAGINE-2 brodalumab 210 mg Q2W group, the median time to PASI 100 was [redacted]; median time to PASI 100 was not estimable in the other groups (43, 44).

Figure 6 PASI 100 response in AMAGINE-2 and AMAGINE-3 (FAS, NRI)



Missing data were imputed as nonresponses (see section B.2.4.4).
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index.
Source: Lebwohl *et al.* 2015 (42).

PASI 90 response

Significantly more patients achieved PASI 90 with brodalumab than with ustekinumab

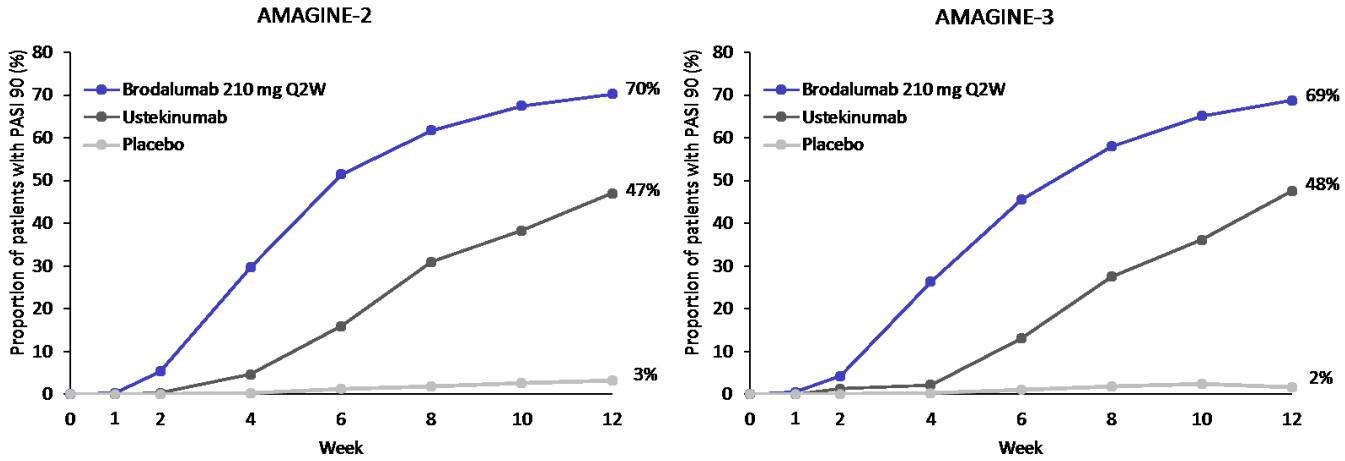
In AMAGINE-2, 70.3% (95% CI, [redacted]%) of patients in the brodalumab 210 mg Q2W group had a 90% improvement in PASI score (PASI 90) at week 12, compared with 47.0% ([redacted]%) of those in the ustekinumab group ($p < 0.001$]). Similarly, in AMAGINE-3, PASI 90 was achieved by 68.8% ([redacted]%) of patients receiving brodalumab 210 mg Q2W and 47.6% ([redacted]%) of those receiving ustekinumab ($p < 0.001$) (40).

As early as week 2, PASI 90 responses were achieved by significantly more patients with brodalumab than with ustekinumab

The response to brodalumab 210 mg Q2W was more rapid than that to ustekinumab (Figure 7), with a significant difference seen as early as week 2: [redacted] receiving brodalumab 210 mg Q2W in AMAGINE-2 and [redacted] in AMAGINE-3 achieved PASI 90 at week 2, compared with [redacted] and [redacted] in the respective ustekinumab groups (43, 44).

In the AMAGINE-2 brodalumab 210 mg Q2W group, the median time to PASI 90 was [redacted] (95% CI, [redacted]) weeks, compared with [redacted] ([redacted]) weeks in the ustekinumab group (43, 44). The corresponding values in AMAGINE-3 were [redacted] ([redacted]) weeks for brodalumab 210 mg Q2W and [redacted] ([redacted]) weeks for ustekinumab (43, 44).

Figure 7 PASI 90 response in AMAGINE-2 and AMAGINE-3 (FAS, NRI)



Missing data were imputed as nonresponses (see section B.2.4.4).
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index.
Source: Lebwohl *et al.* 2015 (42).

PASI 75 response (key secondary endpoint vs ustekinumab)

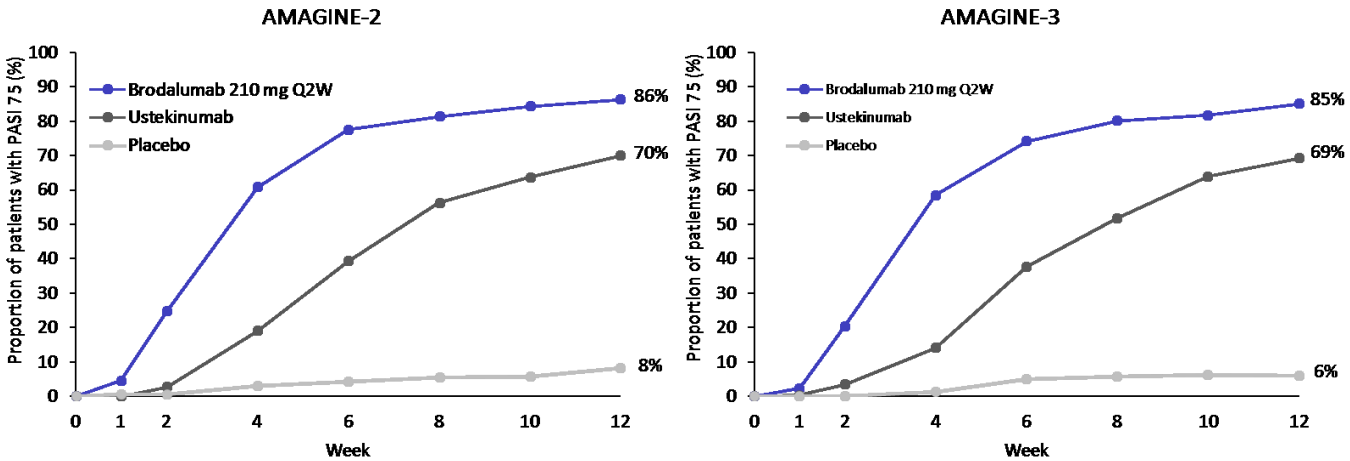
Significantly more patients achieved PASI 75 with brodalumab than with ustekinumab

In AMAGINE-2, 86.3% (95% CI, 83.3–88.9%) of patients in the brodalumab 210 mg Q2W group achieved PASI 75 at week 12, compared with 70.0% (64.5–75.1%) of those in the ustekinumab group ($p < 0.001$). Similarly, in AMAGINE-3, PASI 75 was achieved by 85.1% (82.1–87.8%) of patients treated with brodalumab 210 mg Q2W and 69.3% (63.9−74.4%) of those receiving ustekinumab ($p < 0.001$) (40).

As early as week 1, PASI 75 responses were achieved by significantly more patients with brodalumab than with ustekinumab

The response to brodalumab 210 mg Q2W was more rapid than that to ustekinumab (Figure 8), with a significant difference seen as early as week 1: [redacted] receiving brodalumab 210 mg Q2W in AMAGINE-2 and [redacted] in AMAGINE-3 achieved PASI 75 at week 1, compared with [redacted] and [redacted] in the respective ustekinumab groups (43, 44).

Figure 8 PASI 75 response in AMAGINE-2 and AMAGINE-3 (FAS, NRI)



Missing data were imputed as nonresponses (see section B.2.4.4).
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index.
Source: Lebwohl *et al.* 2015 (42).

The median time to PASI 75 response during the induction phase is shown in Table 15. In both AMAGINE-2 and AMAGINE-3, the median time to PASI 75 with brodalumab 210 mg Q2W was 4.1 weeks, compared with 8.1 weeks with ustekinumab ($p < 0.001$ in both trials) (40).

Table 15 Time to PASI 75 response during the induction phase in AMAGINE-2 and AMAGINE-3 (FAS, as observed)

	AMAGINE-2			AMAGINE-3		
	Placebo N = 309	Ustekinumab N = 300	Brodalumab 210 mg Q2W (N= 612)	Placebo N = 315	Ustekinumab N = 313	Brodalumab 210 mg Q2W (N= 624)
PASI 75 — n (%)	31 (10)	228 (76)	556 (91)	27 (9)	229 (73)	568 (91)
Median time to response, weeks	NE	8.1	4.1	NE	8.1	4.1
95% CI of %	(12.6, NE)	(8.0, 8.3)	(NE, NE)	(NE, NE)	(8.1, 9.9)	(4.1, 4.3)
***p* value vs placebo**	--	--	< 0.001	--	--	< 0.001
***p* value vs ustekinumab**	--	--	< 0.001	--	--	< 0.001

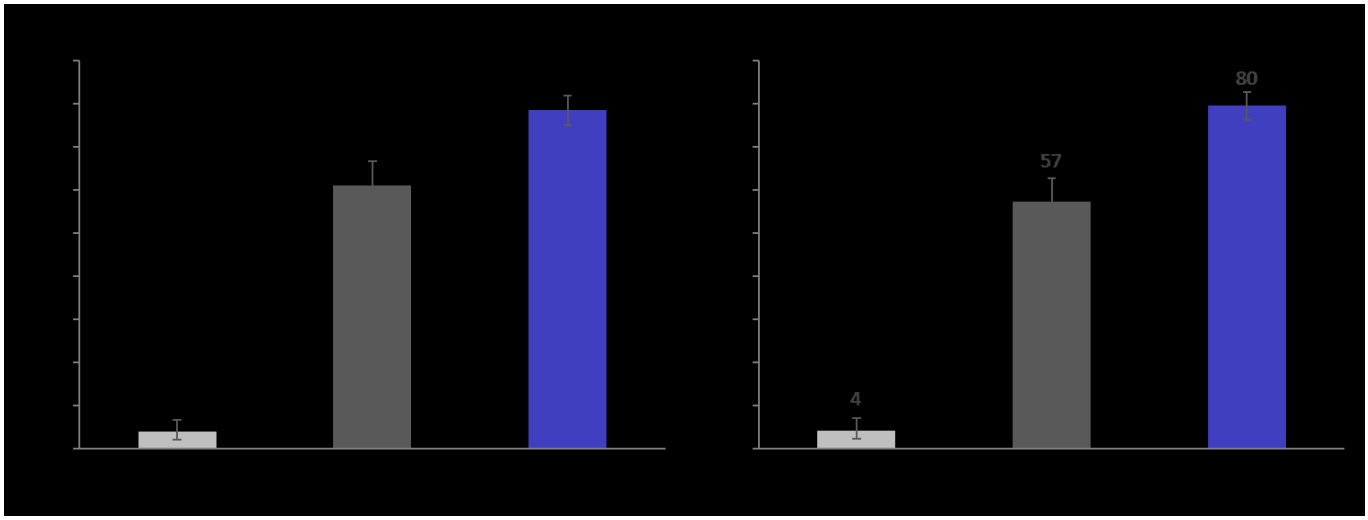
N = Number of patients who were randomised; % = n/N *100
FAS, full analysis set; KM, Kaplan-Meier; CI, confidence interval; NE, not estimable; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks. Source: Lebwohl *et al.* 2015 (40).

sPGA response and sPGA 0

Significantly more patients achieved an sPGA response with brodalumab than with ustekinumab

At baseline, all patients in AMAGINE-2 and AMAGINE-3 had an sPGA score of 3 (moderate disease; Table 10) or above. At week 12, 78.6% (95% CI, 75.1–81.8%) of patients in the AMAGINE-2 brodalumab 210 mg Q2W group achieved an sPGA response (clear [0] or almost clear [1]), compared with 61.0% (55.2–66.6%) of those in the ustekinumab group ($p < 0.001$]). Similarly, in AMAGINE-3, an sPGA response was achieved by 79.6% (76.3–82.7%) of patients treated with brodalumab 210 mg Q2W, compared with 57.2% (51.5–62.7%) of those receiving ustekinumab ($p < 0.001$) (40).

Figure 9 Proportion of patients with an sPGA response at week 12 in AMAGINE-2 and AMAGINE-3 (FAS, NRI)

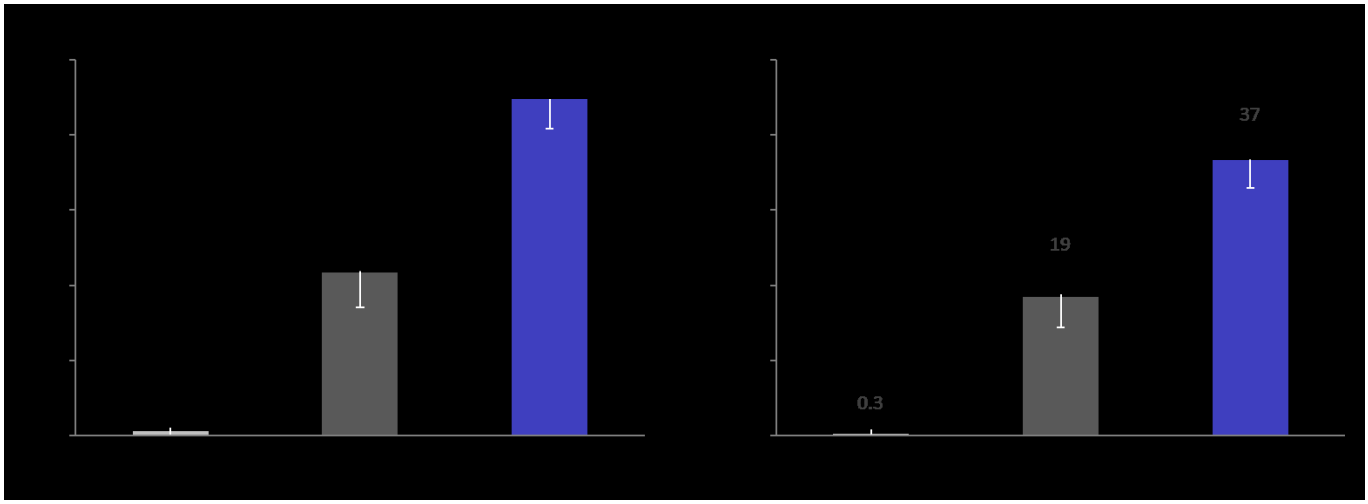


sPGA response was defined as clear (0) or almost clear (1).
Missing data were imputed as nonresponses (see section B.2.4.4).
* $p < 0.001$ vs ustekinumab. † $p < 0.001$ vs placebo. Bars indicate 95% confidence intervals. Q2W, every 2 weeks.
FAS, full analysis set; NRI, non-responder imputation; sPGA, static Physician's Global Assessment.
Source: Lebwohl *et al.* 2015 (42).

Significantly more patients had clear skin, assessed with the sPGA, with brodalumab than with ustekinumab

At week 12 in AMAGINE-2, 44.8% (95% CI, 40.8–48.8%) of patients treated with brodalumab 210 mg Q2W had an sPGA score of 0 (clear skin), compared with 21.7% (95% CI, 17.1–26.8%) of those receiving ustekinumab. The corresponding proportions in AMAGINE-3 were 36.7% (32.9–40.6%) and 18.5% (14.4–23.3%), respectively. In both trials, the difference between brodalumab 210 mg Q2W and ustekinumab was statistically significant ($p < 0.001$) (40).

Figure 10 Proportion of patients with sPGA score of 0 (clear) at week 12 in AMAGINE-2 and AMAGINE-3 (FAS, NRI)



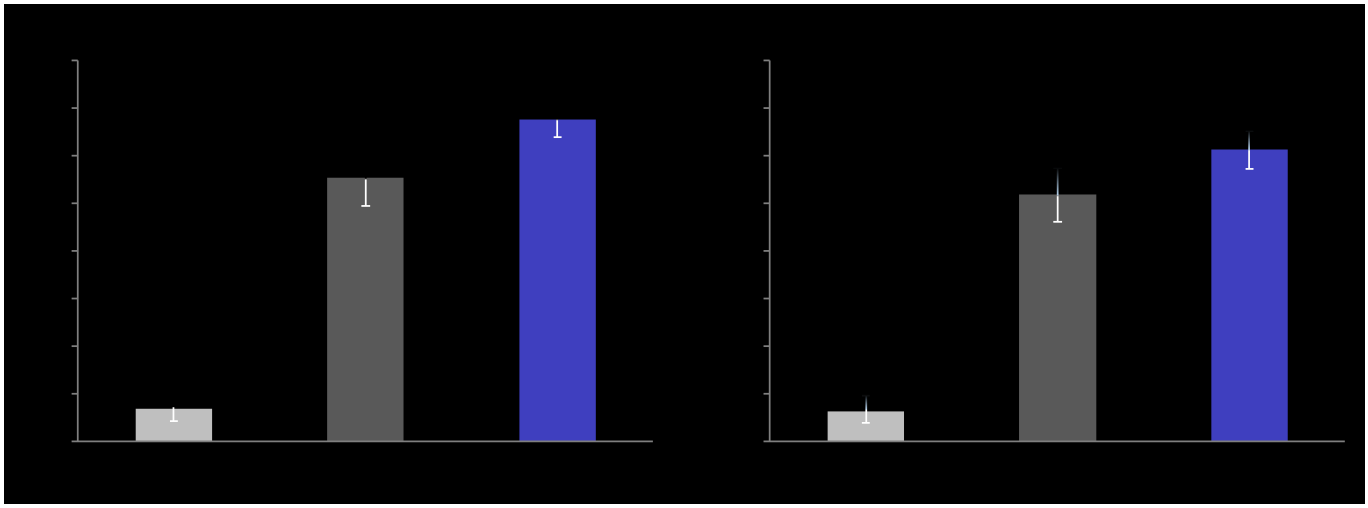
An sPGA score of 0 corresponds to clear skin.
Missing data were imputed as nonresponses (see section B.2.4.4).
* $p < 0.001$ vs ustekinumab. † $p < 0.001$ vs placebo. Bars indicate 95% confidence intervals. Q2W, every 2 weeks.
FAS, full analysis set; NRI, non-responder imputation; sPGA, static Physician's Global Assessment.
Source: Lebwohl *et al*. 2015 (42).

PSI response

A significantly higher proportion of patients treated with brodalumab 210 mg Q2W had a PSI response, compared to ustekinumab or placebo

The responder definition for the PSI used in AMAGINE-2 and AMAGINE-3 was a total score of ≤ 8, with no item scores > 1 (see section B.2.3.1.5, Table 6 for description of PSI). At baseline, the mean PSI scores in the randomised groups in AMAGINE-2 and AMAGINE-3 ranged from 18.6 to 19.0 (Table 10), with fewer than [redacted]% of patients in each group meeting the responder definition (40, 43, 44). At week 12, 67.6% (95% CI, 63.8–71.3%) of patients receiving brodalumab 210 mg Q2W in AMAGINE-2 and 61.2% (57.3–65.1%) in AMAGINE-3 were responders (both $p < 0.001$ vs placebo), compared with 55.3% (49.5–61.0%) and 51.8% (46.1–57.4%), respectively, in the two ustekinumab groups (Figure 11) (40).

Figure 11 Proportion of patients with PSI response in AMAGINE-2 and AMAGINE-3 (FAS, NRI)



PSI response was defined as total score ≤ 8, with no item scores > 1.
Missing data were imputed as nonresponses (see section B.2.4.4).
* $p < 0.001$ vs ustekinumab. † $p < 0.001$ vs placebo. Bars indicate 95% confidence intervals. Q2W, every 2 weeks.
FAS, full analysis set; NRI, non-responder imputation; PSI, Psoriasis Symptom Inventory.
Source: Lebwohl *et al*. 2015 (40).

NAPSI score

Patients receiving brodalumab 210 mg Q2W in AMAGINE-2 and AMAGINE-3 had reductions in NAPSI score at week 12

At baseline, approximately [redacted] of patients in AMAGINE-2 and AMAGINE-3 had nail involvement, defined as a baseline NAPSI score of ≥ 6. Mean NAPSI scores at baseline and week 12 for these patients are shown in Figure 12. Scores at baseline were similar across randomised groups. At week 12, the largest decrease from baseline was observed in the brodalumab 210 mg Q2W group, with smaller decreases in the ustekinumab and placebo groups (43, 44).

Figure 12 Mean NAPSI score at baseline and week 12 in AMAGINE-2 and AMAGINE-3 (FAS, MI)

Analysis includes only patients with baseline NAPSI score of ≥ 6.
Multiple imputation was used to impute missing data.
† $p < 0.001$ vs placebo. No p value for brodalumab 210 mg Q2W vs ustekinumab was calculated.
FAS, full analysis set; MI, multiple imputation; NAPSI, Nail Psoriasis Severity Index.
Source: AMAGINE-2 CSR (43); AMAGINE-3 CSR (44).

B.2.6.2.3 Clinical responses during maintenance phase

As described in section B.2.3.1.1, Figure 4, at week 12, patients receiving placebo in the induction phase were switched to brodalumab 210 mg Q2W in the maintenance phase, while patients receiving ustekinumab in the induction phase continued on ustekinumab maintenance therapy (40).

Patients treated with brodalumab (210 mg Q2W or 140 mg Q2W) in the induction period were re-randomised at week 12 to receive brodalumab maintenance therapy, at doses of either 210 mg Q2W, 140 mg Q2W, 140 mg Q4W or 140 mg Q8W, in a 2:2:2:1 ratio. Therefore, patients treated with brodalumab 210 mg Q2W in the induction phase could either continue to receive brodalumab 210 mg Q2W in the maintenance phase, or could receive an alternative dose of brodalumab (40).

Rescue therapy during maintenance phase

From week 16, patients who did not have an adequate response (i.e., who had a single sPGA score of ≥ 3 or persistent sPGA scores of 2 over at least a 4-week period) received rescue treatment (see section B.2.3.1.1).

Among patients assigned to receive ustekinumab during the maintenance phase, 46% in AMAGINE-2 and 47% in AMAGINE-3 received rescue therapy due to inadequate response (Table 16) (40). In AMAGINE-2, 19% of patients assigned to receive ustekinumab during the maintenance phase were given rescue therapy with brodalumab at week 16; 22% of patients in the AMAGINE-3 ustekinumab maintenance group received brodalumab rescue therapy. A further 27% and 24% of patients in the two ustekinumab maintenance groups received ustekinumab rescue therapy after week 16 (Table 16) (40).

Compared with the ustekinumab groups, fewer patients receiving brodalumab 210 mg Q2W entered rescue (30% and 29% in AMAGINE-2 and AMAGINE-3, respectively; Table 16) (40).

Table 16 Proportion of patients receiving rescue therapy in AMAGINE-2 and AMAGINE-3

	Proportion of patients receiving rescue therapy, n/N (%)	
Maintenance phase treatment group	**AMAGINE-2**	**AMAGINE-3**
Ustekinumab (all rescue therapy)	**46% (133/289)**	**47% (140/301)**
Rescue with brodalumab 210 mg Q2W at week 16	19% (55/289)	23% (69/301)
Rescue with ustekinumab after week 16	27% (78/289)	24% (71/301)
Brodalumab 210 mg Q2W (rescue with brodalumab 210 mg Q2W) [a]	**30% (101/334)**	**29% (100/342)**

[a] Includes all patients re-randomised from brodalumab 210 mg Q2W or brodalumab 140 mg Q2W induction therapy to brodalumab 210 mg Q2W maintenance therapy who subsequently entered rescue.
Q2W, every 2 weeks.
Source: Lebwohl *et al.* 2015 (40).

PASI response at week 52

PASI 75, 90 and 100 responses at week 52 were achieved by significantly more patients treated with brodalumab 210 mg Q2W, compared with ustekinumab

In both AMAGINE-2 and AMAGINE-3, the proportions of patients with PASI 75, PASI 90 and PASI 100 responses at week 52 were higher in the brodalumab 210 mg Q2W group than in the ustekinumab group [redacted]

[redacted]

Table 17 PASI responses at week 52 in AMAGINE-2 and AMAGINE-3 (EAS, NRI)

Outcome	AMAGINE-2		AMAGINE-3	
	Ustekinumab (not re-randomised) (N = 289)	Brodalumab 210 mg Q2W (re-randomised) (N = 334)	Ustekinumab (not re-randomised) (N = 301)	Brodalumab 210 mg Q2W (re-randomised) (N = 342)
PASI 100, n	[redacted]	[redacted]	[redacted]	[redacted]
% (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90, n	[redacted]	[redacted]	[redacted]	[redacted]
% (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75, n	[redacted]	[redacted]	[redacted]	[redacted]
% (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

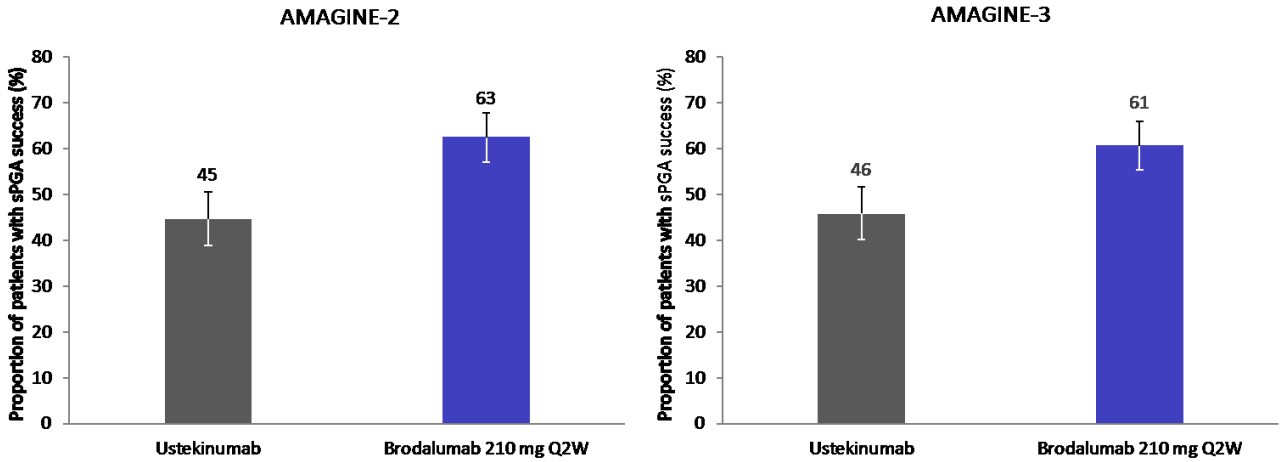
Missing data were imputed as nonresponses (see section B.2.4.4). Patients in all treatment groups with an inadequate response at or before week 52 were imputed as non-responders.
PASI 75, PASI 90 and PASI 100 responses indicate reductions from baseline in the PASI score of ≥ 75%, ≥ 90% and 100%, respectively.
Brodalumab 210 mg Q2W group includes patients initially randomised to placebo or brodalumab 140 mg Q2W and re-randomised to brodalumab 210 mg Q2W.
CI, confidence interval; EAS, efficacy analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks. Source: AMAGINE-2 CSR (43); AMAGINE-3 CSR (44).

Maintenance of sPGA response

Significantly more patients maintained an sPGA response to week 52 with brodalumab 210 mg Q2W than with ustekinumab

The proportion of patients achieving an sPGA response (clear [0] or almost clear [1]) at week 52 was the predefined maintenance endpoint in AMAGINE-2 and AMAGINE-3. At week 52, 62.6% (95% CI, 57.1–67.8%) of patients receiving brodalumab 210 mg Q2W in AMAGINE-2 had an sPGA response, compared with [redacted] of those in the ustekinumab group (Figure 13). Similarly, in AMAGINE-3, an sPGA response was achieved by 60.8% (95% CI, 55.4–60.0%) of patients in the brodalumab 210 mg Q2W group, and [redacted] in the ustekinumab group (43, 44).

Figure 13 Proportion of patients with an sPGA response at week 52 (EAS, NRI)



sPGA response was defined as clear (0) or almost clear (1). Bars indicate 95% confidence intervals.
Missing data were imputed as nonresponses (see section B.2.4.4). Patients with an inadequate response at or before week 52 were conservatively imputed as non-responders at week 52.
EAS, efficacy analysis set; NRI, non-responder imputation; Q2W, every 2 weeks; sPGA, static Physician's Global Assessment. Source: AMAGINE-2 CSR (43); AMAGINE-3 CSR (44).

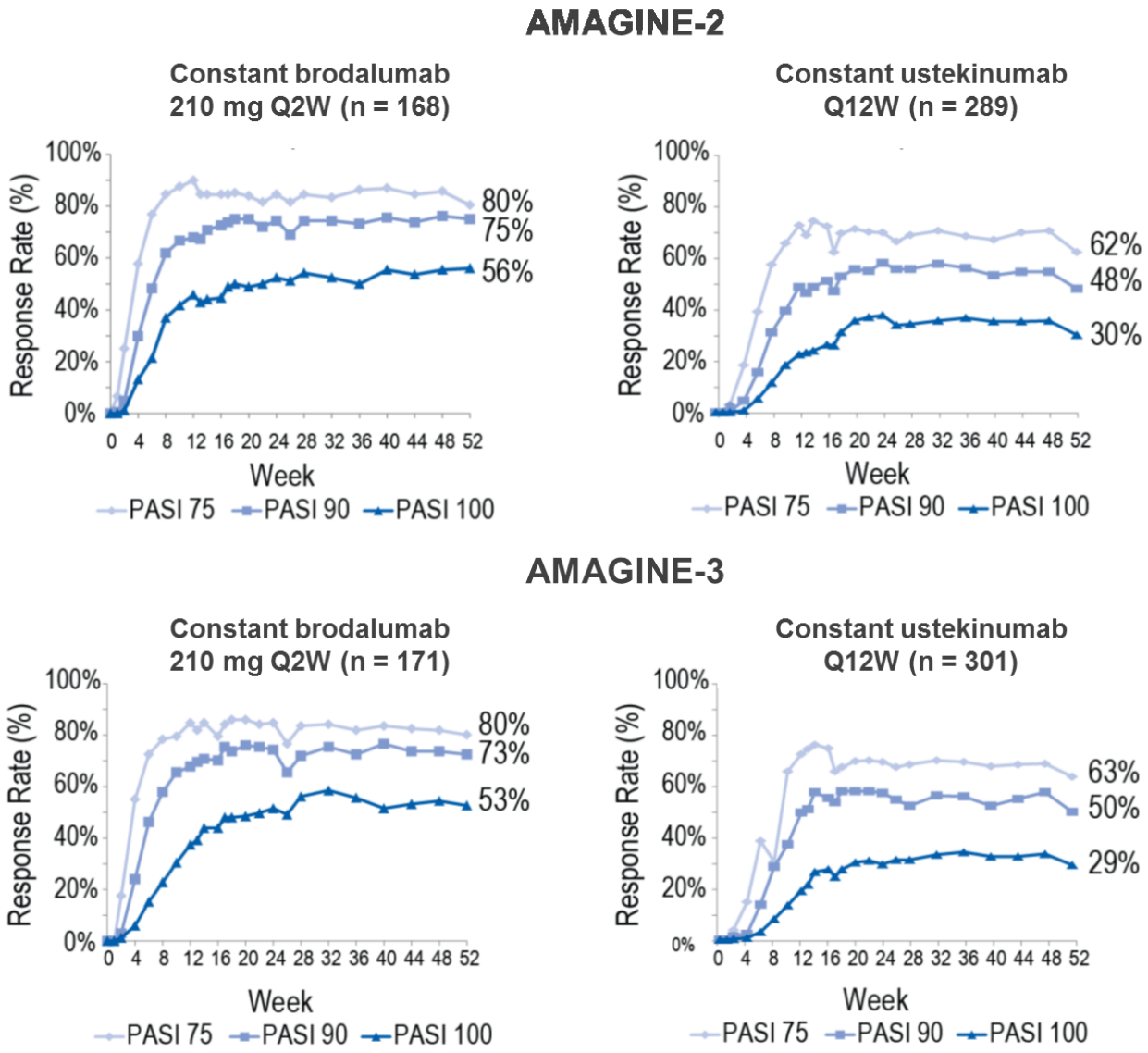
Maintenance of PASI response

For patients receiving constant brodalumab therapy in AMAGINE-2 and AMAGINE-3, PASI responses were maintained to week 52

In total, 189 patients in AMAGINE-2 and 194 in AMAGINE-3 received brodalumab 210 mg Q2W during both the induction phase and maintenance phase (see Appendix L, Table 122 and Table 123). Similarly, 245 patients in AMAGINE-2 and 244 in AMAGINE-3 received constant ustekinumab throughout the study (i.e. these patients were randomised to ustekinumab and did not rescue to brodalumab 210 mg Q2W at week 16) (40).

Among patients receiving constant brodalumab 210 mg Q2W or constant ustekinumab, PASI 75 and PASI 90 response rates at week 12 were maintained to week 52, while PASI 100 response rates increased slightly during the maintenance phase (Figure 14) (40).

Figure 14 PASI 75, PASI 90, and PASI 100 response rates over time to week 52 (EAS patients receiving constant brodalumab 210 mg Q2W or ustekinumab, NRI)



Missing values were imputed as nonresponses (see section B.2.4.4). Patients who qualified for protocol-specified treatment change due to rescue prior to week 52 were imputed as non-responders (including patients in the constant ustekinumab group who rescued with brodalumab at week 16).
EAS, efficacy analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q12W, every 12 weeks.
Source: Lebwohl *et al*. 2015 (40).

Clinical responses in patients switching to brodalumab

In AMAGINE-2, 55 of 300 patients (18%) assigned to receive ustekinumab were given rescue therapy with brodalumab 210 mg Q2W from week 16; 69 of 313 patients (22%) in the AMAGINE-3 ustekinumab group received rescue therapy. In addition, 297 patients in AMAGINE-2 and 298 patients in AMAGINE-3 switched from placebo to brodalumab 210 mg Q2W at week 12. Clinical responses at week 52 for patients switching to brodalumab are shown in Table 18 (40).

Brodalumab was an effective therapy for patients who had had an inadequate response to ustekinumab

Among patients switching from placebo to brodalumab 210 mg Q2W, most achieved PASI 75 and had a PSI response and an sPGA score of 0 or 1; more than half had a PASI 100 response and an sPGA score of 0 (clear). A substantial proportion of patients receiving brodalumab 210 mg Q2W as rescue therapy after having an inadequate response to ustekinumab also had responses at week 52. Most patients had PASI 75 and PSI responses, and the majority had an sPGA score of 0 or 1. In addition, 46% of patients switching from ustekinumab to brodalumab 210 mg Q2W in AMAGINE-2, and 40% in AMAGINE-3, had clear skin (PASI 100 and sPGA 0) at week 52 (40).

Table 18 Clinical responses at week 52 after switching to brodalumab 210 mg Q2W (as observed)

	AMAGINE-2		AMAGINE-3	
Outcome	**Brodalumab 210 mg Q2Wafter placebo N = 297**	**Brodalumab 210 mg Q2W after ustekinumab N = 55**	**Brodalumab 210 mg Q2Wafter placebo N = 298**	**Brodalumab 210 mg Q2W after ustekinumab N = 69**
PASI 75, n/N′ (%)	233/248 (94)	40/44 (91)	240/257 (93)	49/60 (82)
95% CI of %	(90–97)	(78–98)	(90–96)	(70–91)
PASI 100, n/N′ (%)	153/248 (62)	20/44 (46)	174/257 (68)	24/60 (40)
95% CI of %	(55–68)	(30–61)	(62–73)	(28–54)
sPGA 0/1, n/N′ (%)	215/248 (87)	32/44 (73)	231/257 (90)	42/60 (70)
95% CI of %	(82–91)	(57–85)	(86–93)	(57–81)
sPGA 0, n/N′ (%)	153/248 (62)	20/44 (46)	174/257 (68)	24/60 (40)
95% CI of %	(55–68)	(30–61)	(62–73)	(28–54)
PSI response, n/N′ (%)[a]	174/216 (81)	31/37 (84)	188/219 (86)	37/51 (73)
95% CI of %	(75–86)	(68–94)	(81–90)	(58–84)

N = number of patients who entered maintenance phase (or qualified for rescue); N′ = number of patients who had a valid measurement value at the specified week; % = n/N′ x 100;
The brodalumab after placebo group started receiving brodalumab at week 12; the brodalumab after ustekinumab group started receiving brodalumab at week 16.
As observed analysis with no imputation – values may not be directly comparable with other tables (see section B.2.4.4).
[a] PSI response was defined as a total score of ≤ 8 with no item > 1
CI, confidence interval; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: Lebwohl *et al.* 2015 (40).

B.2.6.2.4 HRQoL results

DLQI scores during induction phase

At week 12, patients treated with brodalumab 210 mg Q2W were more likely than those receiving ustekinumab to report psoriasis having no effect at all on their life

At baseline, mean DLQI scores across the randomised groups in AMAGINE-2 and AMAGINE-3 were generally similar (Table 10; AMAGINE-2 range, [redacted]; AMAGINE-3 range, [redacted]). Few patients had a DLQI score of 0 or 1, indicating no effect at all on patient's life ([redacted] across randomised groups) (43, 44).

At week 12, 60.8% (95% CI, [redacted]%) of patients receiving brodalumab 210 mg Q2W in AMAGINE-2, and 59.0% (95% CI, [redacted]%) in AMAGINE-3, had DLQI scores of 0 or 1, compared with 44.3% (95% CI, [redacted]%) and 43.8% (95% CI, [redacted]%) in the two ustekinumab groups (Figure 15). Only 4.5% and 7.0% of patients in the AMAGINE-2 and AMAGINE-3 placebo groups, respectively, had DLQI scores of 0 or 1 at week 12 (43, 44, 67).

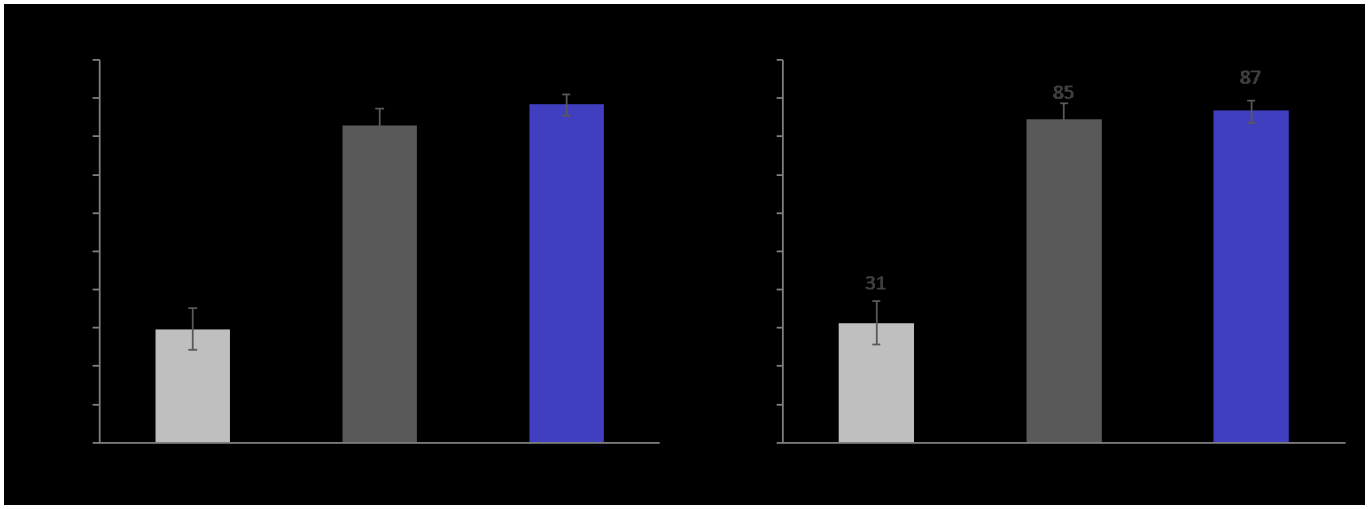
Figure 15 Proportion of patients with DLQI score of 0 or 1 during induction phase (FAS, NRI)

Missing values were imputed as nonresponses (see section B.2.4.4).
† $p < 0.001$ vs placebo.
DLQI, Dermatology Life Quality Index; FAS, full analysis set; NRI, non-responder imputation.
Source: AMAGINE-2 CSR (43); AMAGINE-3 CSR (44).

Most patients treated with brodalumab 210 mg Q2W had a clinically significant 5-point improvement in DLQI score at week 12

At week 12, 88.4% (95% CI, 85.4–90.9%) of patients receiving brodalumab 210 mg Q2W in AMAGINE-2, and 86.7% (95% CI, 83.6–89.4%) in AMAGINE-3, had a clinically meaningful change in DLQI score (≥ 5-point improvement; both $p < 0.001$ vs placebo; Figure 16).

Figure 16 Proportion of patients with ≥ 5-point improvement in DLQI score at week 12 in AMAGINE-2 and AMAGINE-3 (FAS, NRI)



N = number of patients randomised with baseline DLQI ≥ 5.
Missing data were imputed as nonresponses (see section B.2.4.4).
DLQI, Dermatology Life Quality Index; FAS, full analysis set; NRI, non-responder imputation.
† $p < 0.001$ vs placebo. No p value for brodalumab 210 mg Q2W vs ustekinumab was calculated.
Bars indicate 95% confidence intervals. Q2W, every 2 weeks.
Source: AMAGINE-2 CSR (43); AMAGINE-3 CSR (44).

DLQI scores during maintenance phase

DLQI scores of 0 or 1, indicating no effect of psoriasis on a patient's life, were maintained to week 52 in AMAGINE-2 and AMAGINE-3

At week 52, [redacted] of patients receiving maintenance therapy with brodalumab 210 mg Q2W (including patients treated with brodalumab 140 mg Q2W during the induction phase) had DLQI scores of 0 or 1, indicating no effect at all on patient's life; [redacted]

Figure 17 Proportion of patients with DLQI score of 0 or 1 at week 52 in AMAGINE-2 and AMAGINE-3 (EAS, NRI)

[redacted]

Missing data were imputed as nonresponses (see section B.2.4.4). Patients randomised to ustekinumab who switched to brodalumab 210 mg Q2W rescue therapy at week 16 were imputed as non-responders. Patients with an inadequate response at or before week 52 were conservatively imputed as non-responders at week 52. No statistical analysis was performed on these data.
DLQI, Dermatology Life Quality Index; EAS, efficacy analysis set; NRI, non-responder imputation; Q2W, every 2 weeks.
Source: AMAGINE-2 CSR (43); AMAGINE-3 CSR (44).

[redacted]

Figure 18 Proportion of patients switching to brodalumab with DLQI score of 0 or 1 at week 52 in AMAGINE-2 and AMAGINE-3 (as observed)

N = number of patients who entered maintenance phase (or qualified for rescue); % = n/N′ x 100, where N′ = number of patients who had a valid measurement value at the specified week;
The brodalumab after placebo group started receiving brodalumab at week 12; the brodalumab after ustekinumab group started receiving brodalumab at week 16.
As observed analysis with no imputation – values may not be directly comparable with other tables (see section B.2.4.4).
DLQI, Dermatology Life Quality Index; Q2W, every 2 weeks.
Source: AMAGINE-2 CSR (43); AMAGINE-3 CSR (44).

B.2.6.3 AMAGINE-1

B.2.6.3.1 Summary of clinical outcomes in AMAGINE-1

The co-primary endpoints of AMAGINE-1 were the proportion of patients with PASI 75 response at week 12, and the proportion of patients with an sPGA response (defined as clear [0] or almost clear [1]) at week 12. Clinical outcomes in AMAGINE-1 are summarised in Table 19. At week 12, most patients (83%) treated with brodalumab 210 mg Q2W achieved a PASI 75 response, and 76% had an sPGA response – these responses were maintained through to week 52. In addition, 42% of patients receiving brodalumab 210 mg Q2W had a PASI 100 response at week 12. Among patients who had an sPGA response (0 or 1) at week 12 and were re-randomised to continue brodalumab 210 mg Q2W, 67% had completely clear skin (PASI 100) at week 52 (41, 55).

Table 19 Summary of clinical outcomes in AMAGINE-1 (FAS, NRI)

Endpoint	Week 12		Week 52 [a]	
	Placebo (N = 220)	Brodalumab 210 mg Q2W (N = 222)	Placebo (N = 84)	Brodalumab 210 mg Q2W (N = 83)
PASI 100 response, n (%)	1 (0.5)	93 (42) †	0 (0)	56 (67) †
PASI 90 response, n (%)	2 (0.9)	156 (70) †	0 (0)	65 (78) †
PASI 75 response, n (%)	6 (3)	185 (83) †	0 (0)	72 (87)
sPGA 0 (clear), n (%)	1 (0.5)	93 (42) †	0 (0)	56 (67) †
sPGA response (0 or 1), n (%)	3 (1)	168 (76) †	0 (0)	69 (83) †
PSI response, n (%) [b]	9 (4)	135 (61) †		

[a] Patients who received brodalumab 210 mg until week 12, had an sPGA response (0 or 1) at week 12 and were re-randomised to placebo or brodalumab 210 mg.
[b] PSI response was defined as total PSI score ≤ 8, with no individual item score > 1.
† Adjusted *p* value (vs placebo) < 0.001
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: Papp *et al.* 2016 (41); brodalumab SmPC (55); AMAGINE-1 CSR (48).

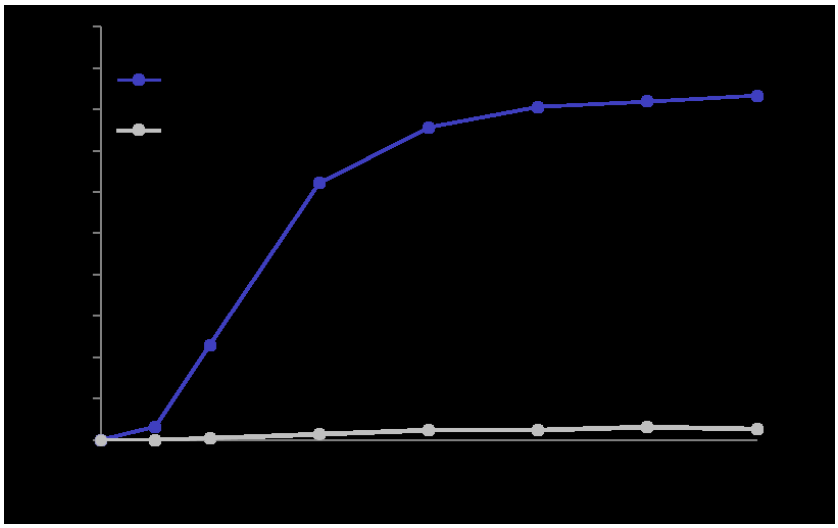
B.2.6.3.2 Clinical responses during induction phase

PASI 75 response (primary endpoint)

Significantly more patients achieved PASI 75 with brodalumab than with placebo

In the brodalumab 210 mg Q2W group, 83.3% (95% CI, 77.8–88.0%) of patients achieved PASI 75 at week 12, compared with 2.7% (1.0–5.8%) of those in the placebo group ($p < 0.001$) (41). The PASI 75 response rate with brodalumab 210 mg Q2W was significantly higher than placebo by week 2, and the median time to PASI 75 was 4.1 weeks (Figure 19) (41).

Figure 19 PASI 75 response in AMAGINE-1 (FAS, NRI)



Missing data were imputed as nonresponses (see section B.2.4.4).
† Adjusted *p* value (vs placebo) < 0.001
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index.
Source: Papp *et al.* 2016 (41).

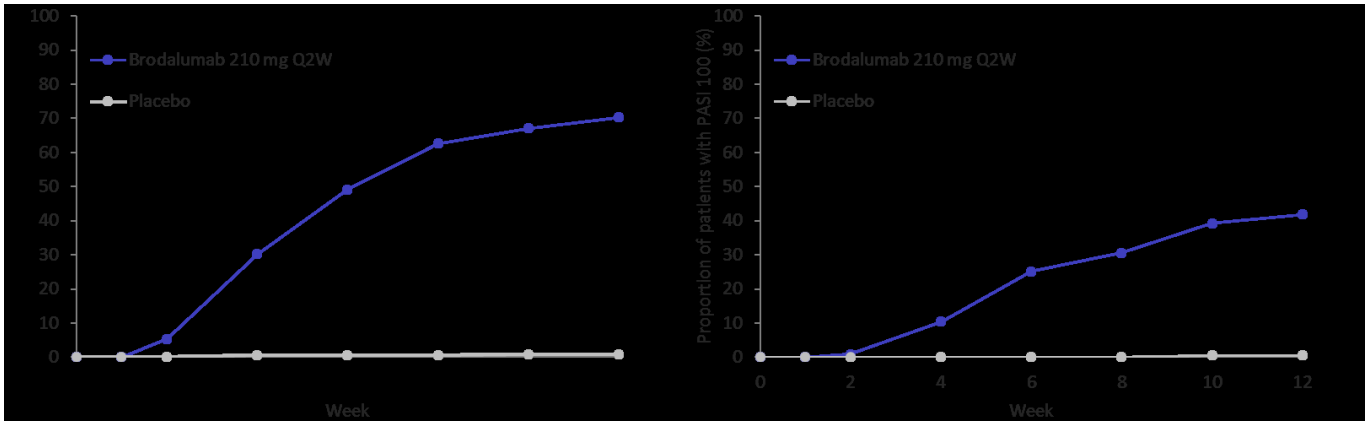
PASI 90 and PASI 100 responses

Significantly more patients achieved PASI 90 and PASI 100 with brodalumab than with placebo

In the brodalumab 210 mg Q2W group, 70.3% (95% CI, 63.8–76.2%) of patients achieved PASI 90 at week 12, and 41.9% (35.3–48.7%) achieved PASI 100 (Figure 20). The corresponding response rates in the placebo group were 0.9% (0.1–3.2%) and 0.5% (0.0–2.5%; $p < 0.001$ for both

comparisons) (41). The median times to PASI 90 and PASI 100 responses with brodalumab 210 mg Q2W were 6.3 weeks and 12.1 weeks, respectively (41).

Figure 20 PASI 90 and PASI 100 responses in AMAGINE-1 (FAS, NRI)



Missing data were imputed as nonresponses (see section B.2.4.4).
† Adjusted *p* value (vs placebo) < 0.001
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index.
Source: Papp *et al*. 2016 (41).

sPGA response and sPGA 0 (primary and key secondary endpoint vs placebo)

Significantly more patients achieved an sPGA response with brodalumab than with placebo

At baseline, all patients in AMAGINE-1 had an sPGA score of 3 (moderate disease; Table 10) or above. At week 12, 75.7% (95% CI, 69.5–81.2%) of patients in the brodalumab 210 mg Q2W group achieved an sPGA response (clear [0] or almost clear [1]), compared with 1.4% (0.3–3.9%) of those in the placebo group ($p < 0.001$) (41). In total, 93 of 222 patients (41.9%) treated with brodalumab 210 mg Q2W had clear skin (sPGA 0) at week 12, compared with 1 of 220 patients (0.5%) in the placebo group (Table 20).

Table 20 sPGA responses at week 12 in AMAGINE-1 (FAS, NRI)

	Week 12	
Endpoint	**Placebo (N = 220)**	**Brodalumab 210 mg Q2W (N = 222)**
sPGA response (0 or 1), n (%)	3 (1.4)	168 (75.7) †
95% CI	0.3–3.9	69.5–81.2
p value vs placebo		< 0.001
sPGA 0 (clear), n (%)	1 (0.5)	93 (41.9) †
95% CI	0.0–2.5	35.3–48.7
p value vs placebo		< 0.001

† Adjusted *p* value (vs placebo) < 0.001
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: Papp *et al.* 2016 (41, 55).

PSSI responses

[redacted]

At baseline, [redacted] patients randomised to placebo and [redacted] randomised to brodalumab 210 mg Q2W in AMAGINE-1 had PSSI scores of ≥ 15. [redacted]

Figure 21 Proportion of patients with PSSI 75 response at week 12 in AMAGINE-1 (FAS, NRI)

Missing data were imputed as nonresponses (see section B.2.4.4).
FAS, full analysis set; NRI, non-responder imputation; PSSI, Psoriasis Scalp Severity Index.
† $p < 0.001$ vs placebo. Bars indicate 95% confidence intervals. Q2W, every 2 weeks.
Source: AMAGINE-1 CSR (48).

B.2.6.3.3 Clinical responses during maintenance phase

At week 12, AMAGINE-1 patients randomised to brodalumab who had an sPGA response (clear [0] or almost clear [1]) were re-randomised to their induction dose of brodalumab or to placebo ('withdrawal'; see section B.2.6.3.4). Among patients treated with brodalumab 210 mg Q2W in the induction phase who were re-randomised to brodalumab 210 mg Q2W (n = 83), most had sustained responses to therapy at week 52, and there was a numerical increase from week 12 in the proportion of patients with PASI 100 responses (Table 21).

Table 21 Clinical responses to brodalumab during the AMAGINE-1 maintenance phase (re-randomised patients with sPGA response at week 12 [n = 83], NRI)

	Brodalumab 210 mg Q2W	
Endpoint	**Week 12**	**Week 52**
sPGA response (0 or 1), n (%)	83 (100)	69 (83) †
PASI 100 response, n (%)	[redacted]	56 (67) †
PASI 90 response, n (%)	[redacted]	65 (78) †
PASI 75 response, n (%)	[redacted]	72 (87) [redacted]

[a] Includes patients who received brodalumab 210 mg until week 12, had an sPGA response (0 or 1) at week 12 and were re-randomised to placebo or brodalumab 210 mg.
[b] PSI response was defined as total PSI score ≤ 8, with no individual item score > 1.
† Adjusted *p* value (vs placebo) < 0.001
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: Papp *et al.* 2016 (41); brodalumab SmPC (55); AMAGINE-1 CSR (48).

B.2.6.3.4 Withdrawal and re-treatment with brodalumab

Re-treatment with brodalumab after loss of response was effective in almost all patients

The design of AMAGINE-1 allowed the efficacy of brodalumab re-treatment after a loss of treatment response to be tested. Among 84 patients with an initial sPGA response on brodalumab 210 mg Q2W who were re-randomised to placebo at week 12, 79 experienced a return of disease (sPGA ≥ 3) during the withdrawal phase. Of these patients, 97% recaptured sPGA response after 12 weeks of re-treatment, and 84% achieved an sPGA score of 0 (clear skin). The median time to recapture sPGA response was 4.1 weeks (Table 22) (41).

Table 22 Median time to recapture response for patients with return of disease during the withdrawal phase in AMAGINE-1 (as observed)

Median time to response, weeks (IQR)	Brodalumab 210 mg Q2W → placebo → brodalumab 210 mg Q2W (*N* = 79)
sPGA response (0 or 1)	4.1 (4.3)
PASI 75	4.1 (2.6)
PASI 90	4.4 (4.3)
PASI 100	8.1 (9.9)

Time to response was calculated as the number of days from qualification for re-treatment to assessment day of first response, divided by 7. Median time to response was calculated using Kaplan-Meier analysis.
IQR, interquartile range; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: Papp *et al.* 2016 (41).

B.2.6.3.5 HRQoL evidence in AMAGINE-1

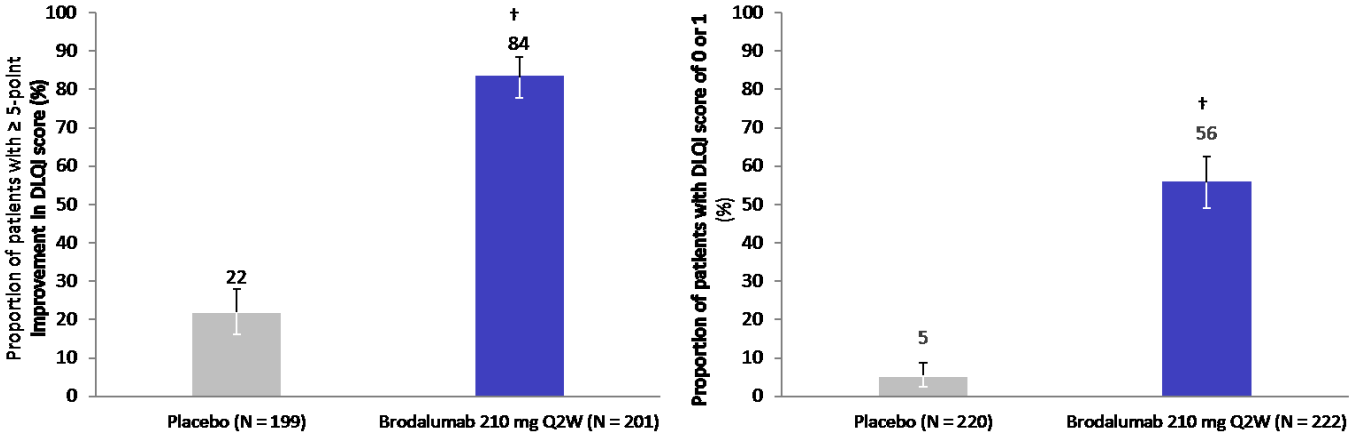
DLQI scores in AMAGINE-1

At baseline, the mean (SD) DLQI score was 14.1 ([redacted]) in the full study population, similar to scores in AMAGINE-2 and AMAGINE-3, and was generally well balanced across the treatment groups. [redacted]

Most patients treated with brodalumab 210 mg Q2W had a clinically meaningful improvement in DLQI scores at week 12, and more than half had scores of 0 or 1

At week 12, significantly more patients treated with brodalumab 210 mg Q2W had a clinically meaningful change in DLQI score (≥ 5-point improvement), compared with those receiving placebo (83.6% vs 21.6%; $p < 0.001$; Figure 22). In addition, more than half of patients in the brodalumab 210 mg Q2W group (55.9%) had DLQI scores of 0 or 1, compared with 5.0% in the placebo group ($p < 0.001$; Figure 22) (48, 67). The proportion of patients treated with brodalumab 210 mg Q2W in AMAGINE-1 who had a DLQI score of 0 or 1 was similar to the results of AMAGINE-2 (60.8%) and AMAGINE-3 (59.0%) (see section B.2.6.2.4) (48, 67).

Figure 22 Proportion of patients with ≥ 5-point improvement in DLQI score (left) and DLQI score of 0 or 1 (right) at week 12 in AMAGINE-1 (FAS, NRI)



N = number of patients randomised, or number randomised with baseline DLQI ≥ 5 (left).
Missing data were imputed as nonresponses (see section B.2.4.4).
DLQI, Dermatology Life Quality Index; FAS, full analysis set; NRI, non-responder imputation.
† $p < 0.001$ vs placebo. Bars indicate 95% confidence intervals. Q2W, every 2 weeks.
Source: Strober *et al.* 2016 (47).

HADS scores in AMAGINE-1

Patients receiving brodalumab 210 mg Q2W in AMAGINE-1 had statistically significant reductions in HADS depression and anxiety scores versus placebo

Baseline HADS scores in AMAGINE-1 were balanced across randomised groups (Table 23), with mean scores in the 'normal' category. During the induction phase, decreases were observed in both the mean HADS depression score and mean anxiety score in the brodalumab 210 mg Q2W group, but not the placebo group. The least squares mean treatment difference was −2.1 for depression and −1.5 for anxiety ($p < 0.001$ for both comparisons) (41).

Table 23 HADS scores at baseline and week 12 in AMAGINE-1 (FAS, MI)

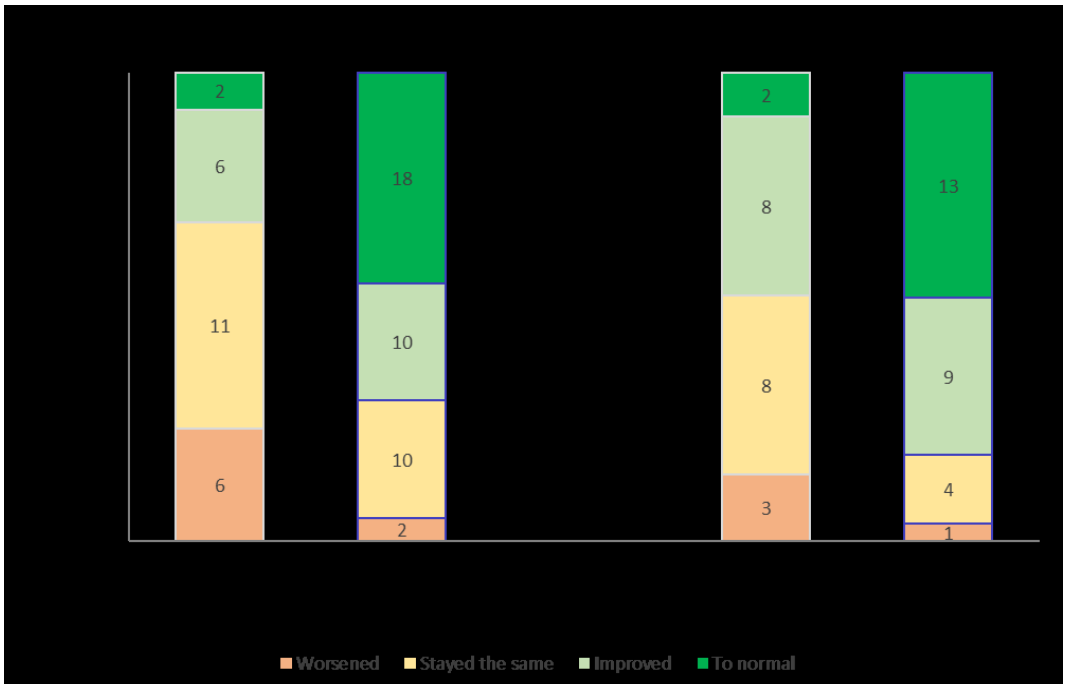
	HADS depression score		HADS anxiety score	
	Placebo (N = 220)	Brodalumab 210 mg Q2W (N = 222)	Placebo (N = 220)	Brodalumab 210 mg Q2W (N = 222)
Baseline HADS score				
Mean ± SD	5.3 ± 3.9	5.5 ± 4.2	6.4 ± 3.8	6.7 ± 4.3
Median (IQR)	5.0 (2.0–8.0)	5.0 (2.0–9.0)	6.0 (4.0–9.0)	6.0 (4.0–9.0)
Week 12 HADS score				
Mean ± SE	5.5 ± 0.3	3.5 ± 0.2	6.3 ± 0.3	4.9 ± 0.3
95% CI	4.9–6.1	3.0–3.9	5.7–6.9	4.4–5.4
Change from baseline, mean (95% CI)	0.2 (–0.2, 0.6)	–2.0 (–1.5, –2.5)	–0.1 (–0.2, 0.5)	–1.8 (–1.3, –2.2)
Difference, LSM ± SE		−2.1 ± 0.3		−1.5 ± 0.3
p value vs placebo		< 0.001		< 0.001

Multiple imputation was used to impute missing data with three imputed datasets.
Data were missing for 5 patients at baseline (placebo, 4; brodalumab 210 mg, 1), and for 4 patients at week 12 (placebo, 3; brodalumab 210 mg, 1).
p values are nominal, without multiplicity adjustment.
CI, confidence interval; FAS, full analysis set; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; LSM, least squares mean; MI, multiple imputation; Q2W, every 2 weeks; SD, standard deviation; SE, standard error.
Source: Papp *et al.* 2016 (41); Papp *et al.* 2016 (68).

HADS scores improved with brodalumab 210 mg among patients with moderate or severe depression and anxiety

At baseline, 27 patients in the AMAGINE-1 placebo group and 42 in the brodalumab 210 mg Q2W group had moderate or severe depression (HADS depression score ≥ 11). In addition, 22 patients receiving placebo and 30 receiving brodalumab 210 mg Q2W had moderate or severe anxiety (41). Among patients with moderate or severe depression, 73% of those receiving brodalumab 210 mg Q2W had improvements in HADS depression score at week 12, with 43% of scores improving to the normal range (0–7) (Figure 23). Similarly, 67% of brodalumab 210 mg Q2W patients with moderate or severe anxiety had improvements, with 42% of scores reducing to normal. For both scales, improvements were numerically more likely with brodalumab 210 mg Q2W than with placebo (Figure 23) (41).

Figure 23 Changes in HADS depression and anxiety scores among patients with moderate or severe scores at baseline in AMAGINE-1 (as observed)



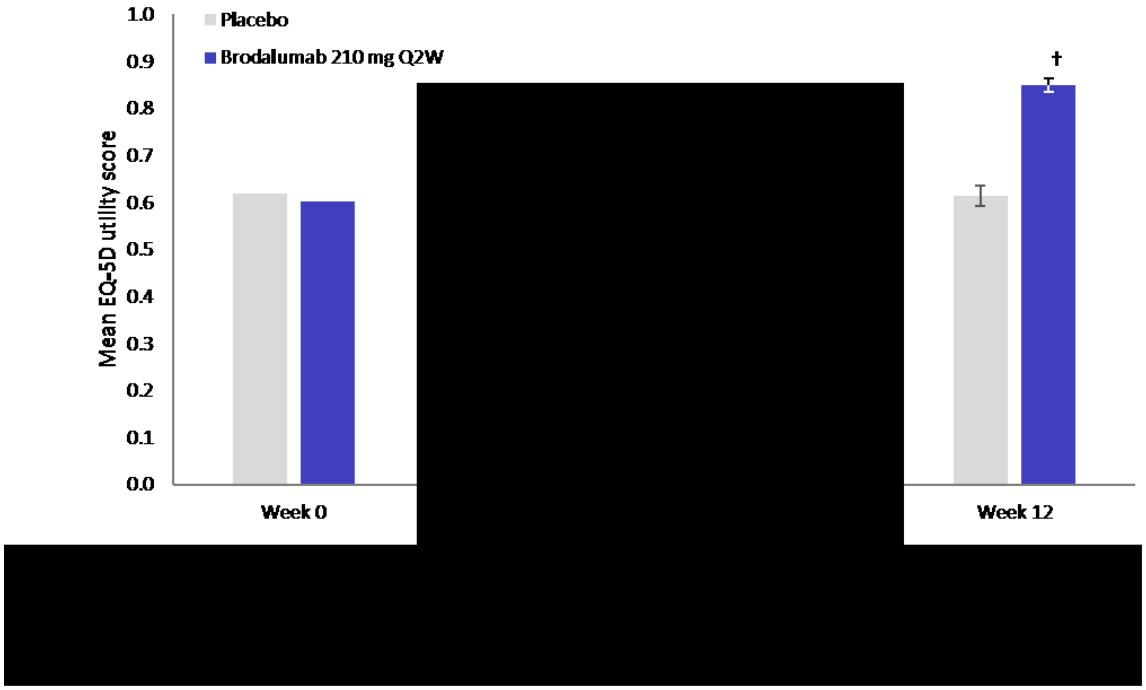
Depression: placebo, 16 moderate and 6 severe; brodalumab 210 mg, 24 moderate and 6 severe at baseline.
Anxiety: placebo, 24 moderate and 3 severe; brodalumab 210 mg, 31 moderate and 11 severe at baseline.
Data are as observed, therefore categories do not add up to the total number of patients.
HADS, Hospital Anxiety and Depression Scale; Q2W, every 2 weeks.
Source: Papp *et al.* 2016 (41).

EQ-5D scores in AMAGINE-1

Patients treated with brodalumab 210 mg Q2W had significant increases in EQ-5D scores versus placebo

At baseline, mean EQ-5D scores in the placebo and brodalumab 210 mg Q2W groups were 0.62 and 0.60, respectively (Figure 24). [redacted] At week 12, there was a statistically significant and clinically relevant difference in mean EQ-5D score between the brodalumab 210 mg Q2W group and the placebo group (0.85 vs 0.61; $p < 0.001$), with a least squares mean difference between groups of [redacted] (48, 69).

Figure 24 EQ-5D utility scores in AMAGINE-1 (FAS, MI)



Multiple imputation was used to impute missing data with three imputed datasets.
† $p < 0.001$ vs placebo. Bars indicate SE.
p values are nominal, without multiplicity adjustment.
EQ-5D, EuroQol-5D questionnaire; FAS, full analysis set; LSM, least squares mean; MI, multiple imputation; Q2W, every 2 weeks; SE, standard error.
Source: Paul *et al.*, 2016 (46); AMAGINE-1 CSR (48).

B.2.6.4 Open-label extension phase, AMAGINE-1, AMAGINE-2 and AMAGINE-3

At week 52, patients treated with ustekinumab in AMAGINE-2 and AMAGINE-3 were switched to receive brodalumab 210 mg Q2W during the open-label extension phase. Patients receiving brodalumab continued to receive brodalumab at the same maintenance or rescue dose (49, 50). Similarly, patients receiving brodalumab in AMAGINE-1 continued to receive brodalumab at the same maintenance or rescue dose (45). PASI and sPGA responses for long-term extension phase participants are summarised in Table 24.

In all three trials, responses to brodalumab 210 mg Q2W during the open-label extension phase were consistent with the results at 52 weeks. The proportion of patients with PASI 75 and PASI 90 responses, with sPGA response, and with complete clearing of psoriasis (PASI 100/sPGA 0) was maintained from week 52 to week 108/120 (45, 49, 50). Extension phase data are as observed, with no imputation; since a number of patients were lost to follow-up (particularly in AMAGINE-2) these observations should be treated with caution.

Table 24 Summary of PASI and sPGA responses during open-label long-term extension phase (as observed)

	Week	Brodalumab 210 mg Q2W		
		AMAGINE-1 (N = 470)	AMAGINE-2 (N = 1392)	AMAGINE-3 (N = 1403)
PASI endpoints				
PASI 75	52 108 120	[redacted]	[redacted]	[redacted]
PASI 90	52 108 120	[redacted]	[redacted]	[redacted]
PASI 100	52 108 120	[redacted]	[redacted]	[redacted]
sPGA endpoints				
sPGA response (0 or 1)	52 108 120	[redacted]	[redacted]	[redacted]
sPGA 0	52 108 120	[redacted]	[redacted]	[redacted]

All data are n/N (%). Data are as observed, with no imputation.
52-week data include patients treated with other doses of brodalumab, or with ustekinumab up to week 52 before changing to brodalumab 210 mg Q2W in the open-label extension phase.
PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: Long-term extension phase CSRs: AMAGINE-1 (45), AMAGINE-2 (49) and AMAGINE-3 (50).

B.2.7 Subgroup analysis

B.2.7.1 Subgroup analyses conducted

Efficacy outcomes were analysed according to the following key subgroups, based on baseline disease severity and therapy history.

- severity of psoriasis (PASI < 20 or ≥ 20 [all patients had baseline PASI > 10])
- severity of psoriasis (DLQI ≤ 10, > 10 or missing)
- previous use of systemic non-biological therapy or phototherapy (yes or no)
- previous use of systemic non-biological therapy (yes or no)
- number of previous systemic non-biological therapies (0, 1 or ≥ 2)
- non-biological systemic agent failure or contraindication (yes or no)
- previous use of psoriasis biological therapy (yes or no)
- previous failure of psoriasis biological therapy (yes or no)
- previous use of anti-TNF therapy (yes or no)

The 'disease severity according to baseline DLQI score' subgroup is a *post hoc* analysis to test the efficacy of brodalumab in a population aligned with the NICE definition of severe disease (see section B.1.3.5) (1). In addition to the pre-planned subgroup 'use of systemic non-biological therapy or phototherapy', 'previous use of systemic non-biological therapy (yes or no)' was added as a *post hoc* subgroup to address the exact subgroup specified in the NICE scope (see section B.1.1). The remaining subgroup analyses were all pre-specified in the trial protocols.

Subgroup analyses were conducted for each of the AMAGINE trial populations individually, and for the pooled patient population (all three trials for brodalumab 210 mg Q2W vs placebo comparisons; AMAGINE-2 and AMAGINE-3 for brodalumab 210 mg Q2W vs ustekinumab comparisons).

Statistical significance was tested using the Cochran-Mantel-Haenszel test stratified by total body weight at baseline (≤ 100 kg, > 100 kg), prior biologic use (yes, no), geographic region, and adjusting for within subgroup baseline PASI score (≤ median, > median), with NRI used to impute missing data.

B.2.7.2 Subgroup analysis results

Detailed subgroup analysis results are shown in Appendix E, Table 91 and Table 92. [redacted]

Overall, the results of the subgroup analyses demonstrate that brodalumab 210 mg Q2W was significantly more efficacious than placebo and ustekinumab regardless of disease severity or prior exposure to systemic therapy, phototherapy and biological therapy.

B.2.8 Meta-analysis

No pairwise meta-analysis was conducted. Head-to-head evidence is not available comparing brodalumab with all of the comparators in the assessment scope; therefore, an NMA was conducted to estimate the relative efficacy of all relevant therapies (see section B.2.9).

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Evidence network for NMA

Head-to-head RCTs between all comparators specified in the NICE scope have not been conducted; therefore, an NMA was undertaken to estimate the relative efficacy between these treatments. NMA can provide comparative measures of effect for all relevant comparators in the absence of direct evidence and is most suitable when there are multi-arm trials included within networks. Use of an NMA in preference to pairwise meta-analysis allowed for the inclusion of all available and relevant evidence, and allowed for more precise treatment effects to be calculated. The results from the NMA feed into the economic model described in section B.3, providing the cost-effectiveness of brodalumab against relevant comparators. This approach has been used in previous NICE STA submissions for biologics in psoriasis (for example ustekinumab, secukinumab and ixekizumab (70-72)).

The NMA results presented in this submission focus on PASI response rates, which are the most relevant efficacy parameter in moderate-to-severe psoriasis, the most consistently reported

outcomes across all studies, and the key efficacy parameter in the cost-effectiveness model (see section B.3).

Full details of the methodology for the NMA are presented in Appendix D.

The SLR described in Appendix D was used to identify all potential studies that may have been relevant for indirect comparison with brodalumab. The inclusion/exclusion criteria for the SLR were sufficiently broad as to identify all potentially relevant studies for the NMA.

In the base case, licensed doses of therapies specified in the scope were included, as well as unlicensed doses and conventional systemic therapies where their inclusion contributed additional indirect evidence for licensed doses. Different dosing schedules of etanercept with 25 mg twice weekly (BIW) and 50 mg weekly (QW) were assumed to have the same clinical efficacy, and the two dosages were pooled into a single etanercept 50 mg per week treatment arm in the base-case results. For all other drugs, different doses and/or dosing regimens were treated as unique comparators.

The base-case network included all these comparators as it allowed for the comprehensive synthesis of direct and indirect evidence for the comparators of interest: biologic therapies, apremilast and DMF. In a sensitivity analysis, only licensed doses which are currently recommended by NICE were included.

The trials used in the base-case NMA are summarised in Table 25, and are described in detail in Appendix D, Table 81, Table 82, Table 83 and Table 84. All studies were connected to the network through common direct comparisons, most often via placebo. All studies were conducted in patients with moderate-to-severe plaque psoriasis who were eligible for systemic therapy. All studies reported data at the end of a short-term induction period, the length of which varied by treatment (infliximab, 10 weeks; brodalumab, etanercept, ixekizumab, secukinumab and ustekinumab, 12 weeks; adalimumab, apremilast and dimethyl fumarate, 16 weeks). Three studies reported outcomes after longer or shorter induction periods (73-75); these included CLEAR (75), a comparison of secukinumab and ustekinumab which reported outcomes at both week 12 and week 16. In the base case, week 12 data from CLEAR (75) were used for consistency with all other secukinumab and ustekinumab trials. The effect of using 16-week outcomes was tested in sensitivity analysis 2 (see section B2.9.3).

Table 25 Summary of the trials used to carry out the NMA

Trial / Comparator	Brodalumab	Adalimumab	Apremilast	Etanercept	Infliximab	Ixekizumab	Secukinumab	Ustekinumab	DMF	Placebo	Other therapies [a]
AMAGINE-1, Papp *et al*., 2016 and LEO Pharma CSR (41, 48)	✓									✓	
AMAGINE-2, Lebwohl *et al*., 2015 and LEO Pharma CSR (40, 43)	✓							✓		✓	
AMAGINE-3, Lebwohl *et al*., 2015 and LEO Pharma CSR (40, 44)	✓							✓		✓	
Nakagawa *et al*., 2016 (51)	✓									✓	
Papp *et al*., 2012 (52)	✓									✓	
CHAMPION, Saurat *et al*. 2008 (76)		✓								✓	✓
Goldminz *et al*.,2015 (77)		✓									✓
Cai *et al*., 2016 (74)		✓								✓	
REVEAL, Menter *et al*., 2008 (78)		✓								✓	
Asahina *et al*., 2010 (79)		✓								✓	
Gordon *et al*., 2006 (80)		✓								✓	
X-PLORE, Gordon *et al*., 2015 (42)		✓								✓	
Bissonnette *et al*., 2013 (81)		✓								✓	
VOYAGE 1, Blauvelt *et al*., 2017 (82)		✓								✓	✓
VOYAGE 2, Reich *et al*., 2017 (83)		✓								✓	✓
PSOR-005, Papp *et al*., 2012 (84)			✓							✓	
ESTEEM 1, Papp *et al*., 2015 (85)			✓							✓	
ESTEEM 2, Paul *et al*., 2015 (86)			✓							✓	
Papp at al., 2013 (87)			✓							✓	
Ohtsuki *et al*., 2017 (88)			✓							✓	
LIBERATE, Reich 2016 (89)			✓	✓						✓	
Leonardi *et al*., 2003 (90)				✓						✓	
Gottlieb *et al*., 2003 (91)				✓						✓	
Papp *et al*., 2005 (92)				✓						✓	
Van de Kerkhof, 2008 (93)				✓						✓	
Bagel 2012 (94)				✓						✓	
Bachelez 2015 (95)				✓						✓	✓
Tyring, 2006 (96)				✓						✓	
PRISTINE, Strohal *et al* 2013 (97) [b]				✓							
M10-114, Gottlieb 2011 (98)				✓						✓	✓
M10-315 (99)				✓						✓	✓
reSURFACE2 (100)				✓						✓	✓
PIECE, De Vries 2016 (101)				✓	✓						
Yang 2012 (102)					✓					✓	
EXPRESS, Reich 2005(103)					✓					✓	
Chaudhari 2001 (104)					✓					✓	
SPIRIT, Gottlieb 2004, (105)					✓					✓	

Trial / Comparator	Brodalumab	Adalimumab	Apremilast	Etanercept	Infliximab	Ixekizumab	Secukinumab	Ustekinumab	DMF	Placebo	Other therapies [a]
EXPRESS II, Menter 2007 (106)					✓					✓	
Torii 2010(107)					✓					✓	
RESTORE1, Barker 2011 (73)					✓						✓
UNCOVER-1, Gordon 2016 and NICE STA (72, 108)						✓				✓	
UNCOVER-2, Griffiths 2015 (109)				✓		✓				✓	
UNCOVER-3, Griffiths 2015(109)				✓		✓				✓	
IXORA-S, Reich *et al*. 2017						✓		✓			
FEATURE, Blauvelt 2015 and Novartis Submission for NICE STA (71, 110)							✓			✓	
ERASURE, Langley 2014 and Clinicaltrials.gov (111, 112)							✓			✓	
FIXTURE, Langley 2014 and NICE STA (71, 111)				✓			✓			✓	
JUNCTURE, Paul 2015 and NICE STA (71, 113)							✓			✓	
SCULPTURE, Mrowietz 2015 and Clinicaltrials.gov (114, 115) [c]							✓				
CLEAR, Thaci 2015 (75)							✓	✓			
PEARL, Tsai 2011 (116)								✓		✓	
PHOENIX-1, Leonardi 2008 (117)								✓		✓	
PHOENIX-2, Papp 2008 (118)								✓		✓	
LOTUS, Zhu 2013 (119)								✓		✓	
ACCEPT, Griffiths 2010(120)				✓				✓			
Igarashi 2012(121)								✓		✓	
BRIDGE, Mrowietz *et al*. 2017 (122)									✓	✓	✓
Caproni 2009 (26)				✓							✓
Gisondi 2008 (123)				✓							✓

[a] Other therapies are methotrexate (73, 76, 77), guselkumab (82, 83), tofacitinib (95), briakinumab (98, 99), tildrakizumab (100), fumaderm (122) and acitretin (26, 123).
[b] The PRISTINE trial compared etanercept 50 mg weekly and twice weekly.
[c] The SCULPTURE trial compared secukinumab 150 mg and 300 mg.

B.2.9.2 Base-case NMA

The base-case analysis of PASI response outcomes included data from 59 RCTs involving 28,346 patients. The network diagram of included evidence in the base-case analysis is presented in Figure 25. Forty-five of these studies, involving 18,106 patients, met the stricter inclusion criteria for the sensitivity analysis in which only licensed and recommended therapies were included (see section B.2.9.3).

Results of the base-case NMA, in terms of the probability of achieving each level of PASI response for each treatment, are summarised in Table 26. Risk ratios are presented in Table 27 for each drug compared with placebo and in Table 28 for brodalumab 210 mg versus other treatments. Estimates of effect (probit scale) for all treatments relative to placebo are presented in Figure 26.

In the base-case analysis, brodalumab 210 mg Q2W was shown to be significantly more efficacious at inducing all levels of PASI response than, adalimumab 40 mg Q2W, apremilast 30 mg BID, etanercept 50 mg weekly, infliximab 5 mg/kg, secukinumab 300 mg, ustekinumab (45 mg, 90 mg, and dosing as per label) and DMF, as well as all of the conventional systemic therapies in the network. The efficacy of brodalumab 210 mg Q2W was not significantly different from that of ixekizumab 80 mg Q2W (Table 28).

Figure 25 Network diagram of evidence included in the base-case NMA – all treatments including unlicensed doses and conventional systemic therapies

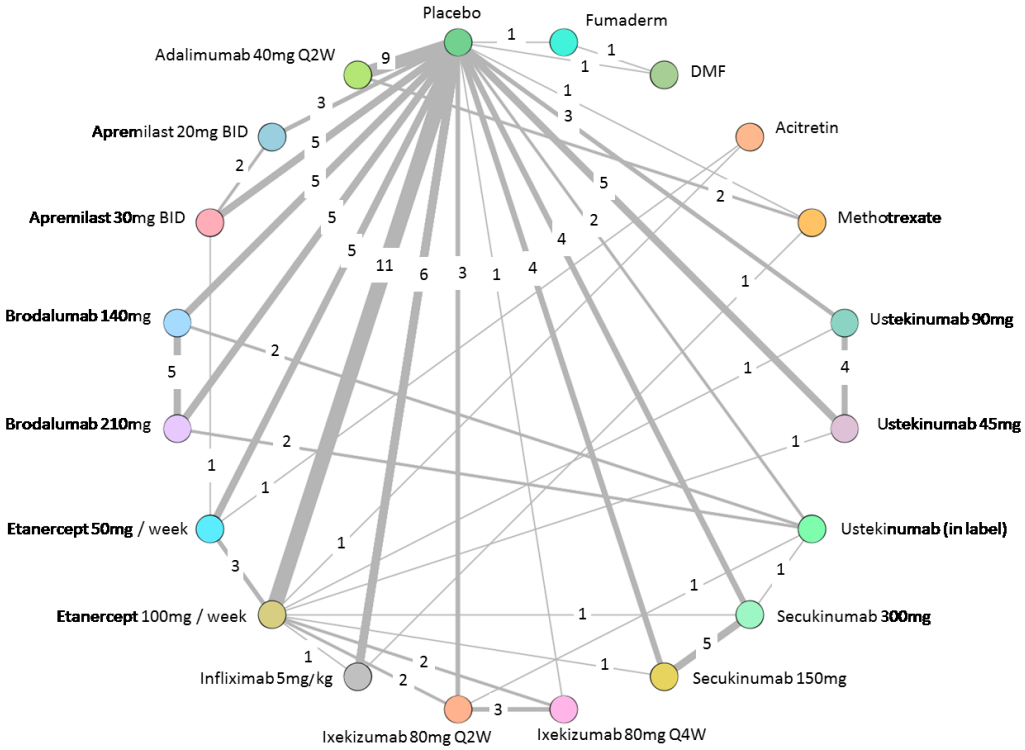


Table 26 Predicted PASI responses for evaluated interventions – base case

Treatment	Probability of PASI response, median (95% CrI)			
	PASI 50	PASI 75	PASI 90	PASI 100
Placebo	14.7% (12.5-17.2)	5.7% (4.6-7.1)	1.3% (1-1.6)	0.1% (0.1-0.2)
Brodalumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]
Brodalumab 210mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg Q2W	82.6% (77.7-86.7)	66% (59.3-72.1)	40% (33.4-46.9)	14.8% (11.1-19.2)
Apremilast 20mg BID	*36.8% (27.9-46.2)*	*19.4% (13.3-26.7)*	*6.3% (3.8-9.9)*	*1% (0.5-1.9)*
Apremilast 30mg BID	46.9% (39.7-54.3)	27.3% (21.5-33.7)	10.3% (7.3-13.9)	2% (1.2-3)
Etanercept 50 mg / week	59.9% (52.9-66.7)	39.1% (32.5-46.2)	17.4% (13.2-22.4)	4.2% (2.8-6)
Etanercept 100 mg / week	*73% (68.2-77.4)*	*53.4% (47.8-58.9)*	*28.1% (23.6-33.1)*	*8.5% (6.5-10.9)*
Infliximab 5mg/kg	91% (87.1-94)	79.2% (72.8-84.7)	55.9% (47.7-64.1)	26% (19.7-33.3)
Ixekizumab 80mg Q4W	*95% (92.8-96.6)*	*86.8% (82.5-90.3)*	*67.5% (60.7-73.8)*	*36.7% (30.1-43.8)*
Ixekizumab 80mg Q2W	96.6% (95.1-97.8)	90.4% (87-93)	73.9% (67.9-79.2)	43.9% (37.2-50.9)
Secukinumab 150mg	*87% (82.7-90.5)*	*72.5% (66.1-78.3)*	*47.4% (40.2-54.7)*	*19.5% (14.8-25)*
Secukinumab 300mg	93.4% (90.9-95.4)	83.6% (79-87.7)	62.4% (55.7-69)	31.6% (25.7-38.3)
Ustekinumab 45mg	86.4% (82.3-89.8)	71.6% (65.5-77.1)	46.3% (39.5-53.2)	18.8% (14.5-23.8)
Ustekinumab 90mg	88.7% (84.9-91.9)	75.3% (69.3-80.7)	50.9% (43.6-58.1)	22% (17-27.8)
Ustekinumab (in-label dose)	86% (81.7-89.6)	71% (64.7-76.8)	45.6% (38.7-52.7)	18.3% (14-23.4)
DMF	36.7% (24.9-50)	19.3% (11.4-29.9)	6.3% (3.1-11.7)	1% (0.4-2.4)
Fumaderm	*43% (30.4-56.6)*	*24.1% (14.9-35.9)*	*8.6% (4.4-15.3)*	*1.5% (0.6-3.4)*
Methotrexate	*56.4% (46.1-65.9)*	*35.7% (26.5-45.3)*	*15.1% (9.8-21.8)*	*3.4% (1.9-5.8)*
Acitretin	*44% (25.2-64)*	*24.9% (11.6-43.3)*	*9% (3.1-20.3)*	*1.6% (0.4-5.2)*

Therapies other than the comparators of interest are shown in italics.
BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

Figure 26 **Median treatment effects (95% credible intervals) for interventions versus placebo – base case**

[redacted]

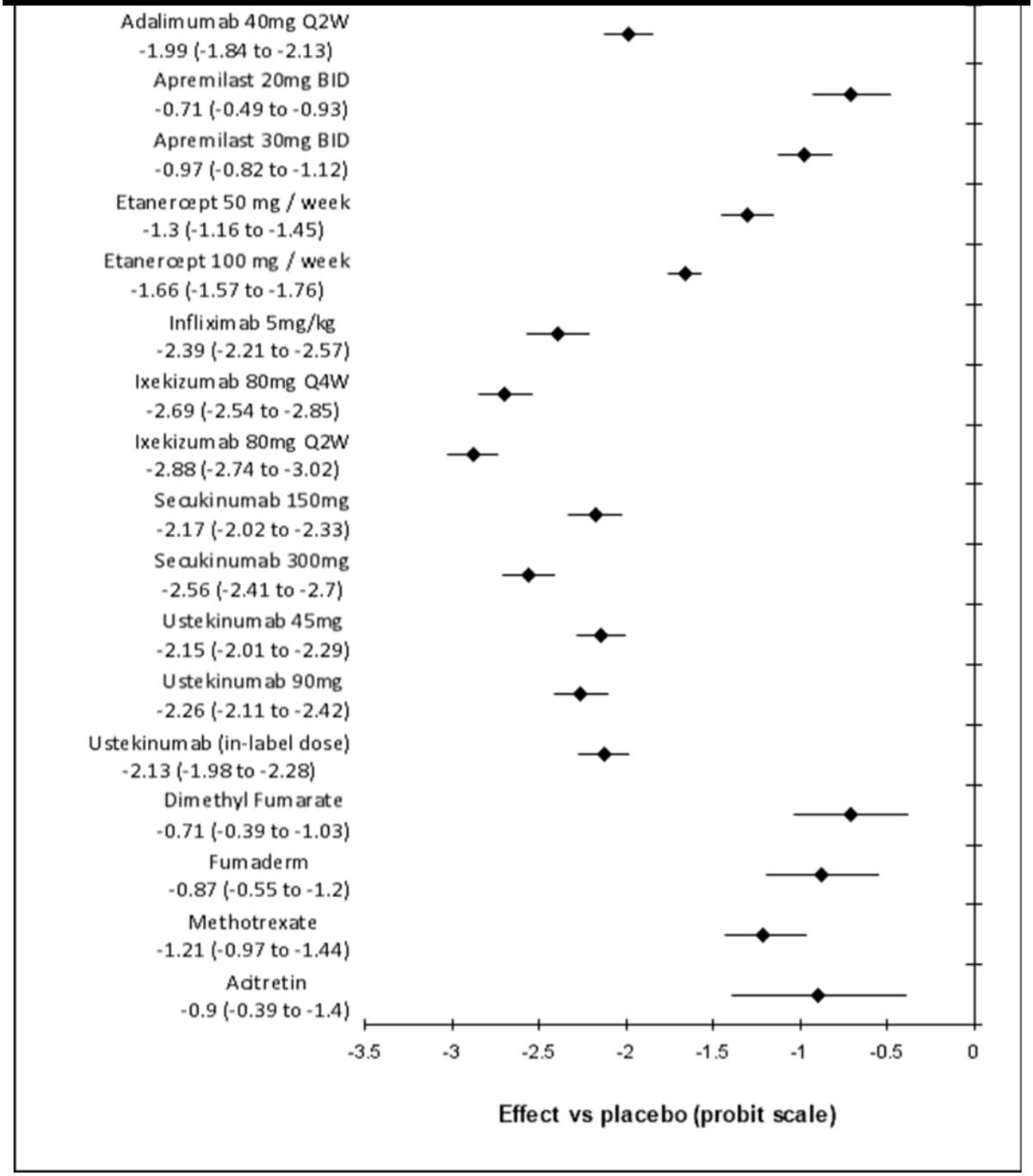


Table 27 Treatment effects at each level of PASI response for interventions versus placebo – base case

Treatment	Risk ratio versus placebo, median (95% Credible Interval)			
	PASI 50	PASI 75	PASI 90	PASI 100
Brodalumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]
Brodalumab 210mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg Q2W	5.61 (4.91 to 6.44)	11.45 (9.69 to 13.61)	31.82 (25.61 to 39.69)	121.9 (91.06 to 163)
Apremilast 20mg BID	*2.5 (1.94 to 3.12)*	*3.36 (2.39 to 4.56)*	*5.03 (3.15 to 7.67)*	*8.36 (4.47 to 14.81)*
Apremilast 30mg BID	3.19 (2.74 to 3.69)	4.74 (3.85 to 5.78)	8.16 (6.1 to 10.72)	16.24 (10.93 to 23.57)
Etanercept 50 mg / week	4.06 (3.57 to 4.66)	6.79 (5.69 to 8.15)	13.81 (10.8 to 17.71)	34.27 (24.45 to 48.19)
Etanercept 100 mg / week	*4.96 (4.4 to 5.61)*	*9.27 (8.01 to 10.81)*	*22.37 (18.65 to 27.07)*	*70.13 (55.58 to 89.2)*
Infliximab 5mg/kg	6.18 (5.36 to 7.16)	13.74 (11.48 to 16.58)	44.42 (35.13 to 56.51)	213.8 (155.7 to 295.2)
Ixekizumab 80mg Q4W	*6.45 (5.57 to 7.52)*	*15.08 (12.55 to 18.25)*	*53.68 (42.73 to 67.92)*	*302.7 (226.8 to 406.9)*
Ixekizumab 80mg Q2W	6.57 (5.66 to 7.67)	15.71 (13.02 to 19.08)	58.75 (46.63 to 74.63)	361.9 (272.2 to 486.3)
Secukinumab 150mg	*5.9 (5.15 to 6.82)*	*12.59 (10.6 to 15.08)*	*37.65 (30.16 to 47.39)*	*160.8 (119.5 to 217.9)*
Secukinumab 300mg	6.34 (5.49 to 7.38)	14.53 (12.14 to 17.52)	49.61 (39.68 to 62.6)	261 (196.4 to 350.3)
Ustekinumab 45mg	5.87 (5.12 to 6.76)	12.43 (10.49 to 14.84)	36.79 (29.63 to 45.99)	154.8 (116.4 to 206.5)
Ustekinumab 90mg	6.02 (5.24 to 6.97)	13.08 (10.99 to 15.69)	40.42 (32.34 to 50.89)	181.5 (135.1 to 245.2)
Ustekinumab (in-label dose)	5.84 (5.1 to 6.72)	12.32 (10.4 to 14.71)	36.22 (29.13 to 45.4)	150.7 (112.9 to 202.6)
Dimethyl Fumarate	2.49 (1.73 to 3.39)	3.35 (2.04 to 5.16)	5.01 (2.55 to 9.14)	8.31 (3.37 to 18.97)
Fumaderm	*2.92 (2.1 to 3.84)*	*4.18 (2.66 to 6.19)*	*6.83 (3.64 to 11.92)*	*12.7 (5.41 to 27.61)*
Methotrexate	*3.82 (3.14 to 4.56)*	*6.2 (4.68 to 7.94)*	*12.05 (8.05 to 17.15)*	*28.17 (16.05 to 46.3)*
Acitretin	*2.99 (1.74 to 4.36)*	*4.32 (2.05 to 7.51)*	*7.14 (2.57 to 15.97)*	*13.51 (3.41 to 42.16)*

Therapies other than the comparators of interest are shown in italics.
BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 28 Treatment effects at each level of PASI response for brodalumab 210 mg vs comparators – base case

Treatment	Risk ratio brodalumab 210 mg versus comparator, median (95% CrI)			
	PASI 50	PASI 75	PASI 90	PASI 100
Brodalumab 140mg				
Adalimumab 40mg Q2W				
Apremilast 20mg BID				
Apremilast 30mg BID				
Etanercept 50 mg / week				
Etanercept 100 mg / week				
Infliximab 5mg/kg				
Ixekizumab 80mg Q4W				
Ixekizumab 80mg Q2W				
Secukinumab 150mg				
Secukinumab 300mg				
Ustekinumab 45mg				
Ustekinumab 90mg				
Ustekinumab (in-label dose)				
Dimethyl Fumarate				
Fumaderm				
Methotrexate				
Acitretin				

Therapies other than the comparators of interest are shown in italics.
Risk ratios in bold indicate statistically significant differences.
[a] 95% credible interval does not span 1.
BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

B.2.9.3 Sensitivity analyses to address uncertainties in the NMA inputs

B.2.9.3.1 Sensitivity analyses conducted

Sensitivity analyses were performed to test alternative inclusion criteria for compared treatments, minimum sample size and indicators of disease severity:

- **Sensitivity analysis 1:** In the base-case NMA, conventional systemic therapies and unlicensed doses of therapies specified in the scope were included where this provided additional indirect evidence for the comparators of interest. In this sensitivity analysis, only EMA licensed doses which are currently recommended by NICE were included.

- **Sensitivity analysis 2:** The base-case analysis used 12-week outcomes from the CLEAR trial (75) because these were more directly comparable to the results of the other secukinumab and ustekinumab trials. However, the primary endpoint of CLEAR was the proportion of patients with a PASI 90 response at week 16. Therefore, in this sensitivity analysis 16-week outcomes from CLEAR were used.
- **Sensitivity analysis 3:** Studies which randomised fewer than 100 patients were excluded from the analysis in order to reduce the potential risk of bias caused by Type I error.
- **Sensitivity analysis 4:** Studies in which more than 30% of randomised patients reported having previously tried biological therapy were excluded from the analysis.
- **Sensitivity analysis 5:** Studies with a mean baseline PASI score of greater than 25 were excluded from the analysis.

B.2.9.3.2 Sensitivity analysis results

Sensitivity analysis 1

Forty-five of the studies in the base-case network, involving 18,106 patients, met the stricter inclusion criteria for sensitivity analysis 1, which only included licensed and recommended therapies. The network diagram of included evidence in sensitivity analysis 1 is shown in Figure 25.

The results of sensitivity analysis 1 were similar to the base case (Table 29). Compared with the base-case analysis, there was a slight increase in the expected efficacy of infliximab, decreasing the magnitude of the brodalumab 210 mg vs infliximab risk ratio. In this analysis there were no statistically significant differences between brodalumab 210 mg and infliximab or between brodalumab 210 mg and secukinumab 300 mg.

Sensitivity analysis 2

In this sensitivity analysis, 16-week outcomes reported in the CLEAR study (75) were used instead of the 12-week outcomes which were used in the base case. PASI 75, PASI 90 and PASI 100 outcomes at week 16 were 93.1%, 79.0% and 44.3% for secukinumab 300 mg and 82.7%, 57.6% and 28.4% for ustekinumab, respectively (75). The results of the analysis using 16-week data were similar to the base case (Table 30), except that the difference between brodalumab 210 mg and secukinumab 300 mg was no longer statistically significant.

Sensitivity analyses 3–5

The results of sensitivity analyses excluding studies with fewer than 100 patients, in which more than 30% of patients had used previous biological therapy, or in which the mean baseline PASI score was greater than 25 were all similar to the base-case analysis; these results are not described in detail in this submission.

Figure 27 Network diagram of evidence included in sensitivity analysis 1 –licensed doses of relevant comparators only

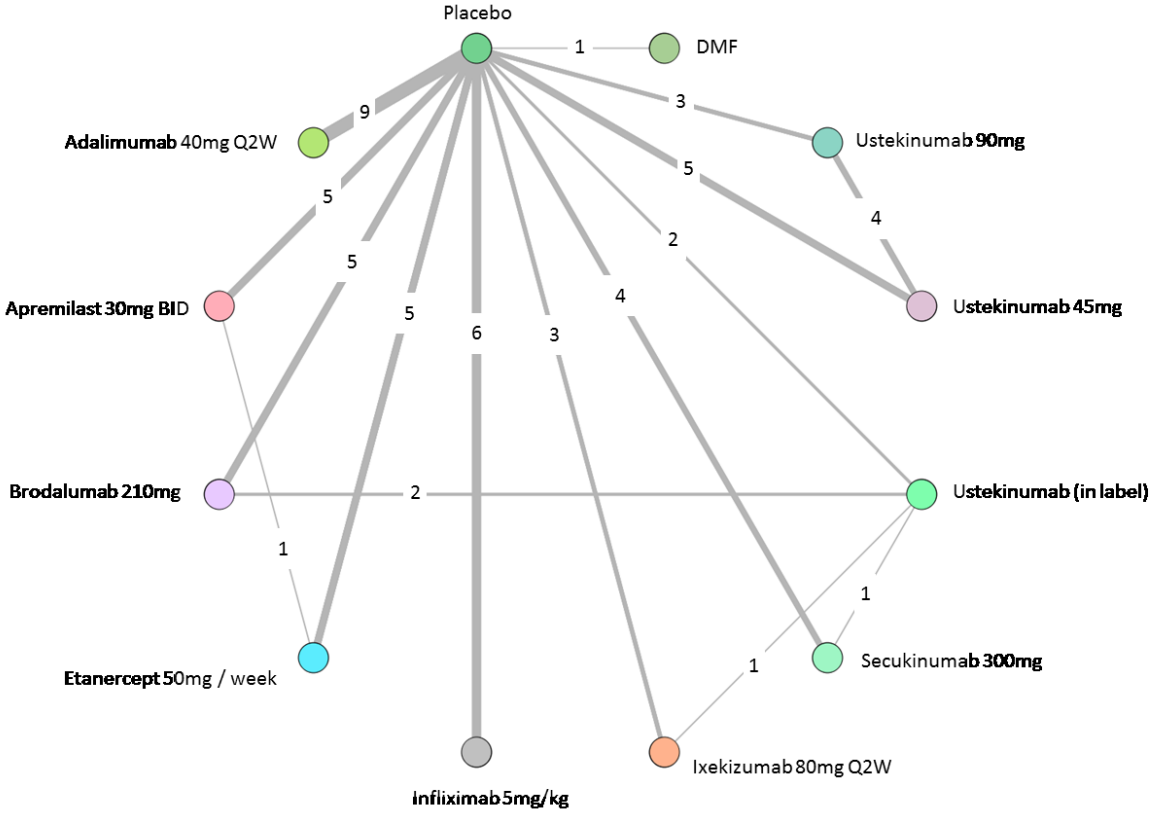


Table 29 Treatment effects at each level of PASI response for brodalumab 210 mg vs comparators – sensitivity analysis 1

Treatment	Risk ratio brodalumab 210 mg versus comparator, median (95% CrI)			
	PASI 50	PASI 75	PASI 90	PASI 100
Placebo				
Adalimumab 40mg Q2W				
Apremilast 30mg BID				
Etanercept 50 mg / week				
Infliximab 5mg/kg				
Ixekizumab 80mg Q2W				
Secukinumab 300mg				
Ustekinumab 45mg				
Ustekinumab 90mg				
Ustekinumab (in-label dose)				
Dimethyl Fumarate				

Risk ratios in bold indicate statistically significant differences.
[a] 95% credible interval does span 1.
BID, twice daily; CrI, credible interval; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks.

Table 30 Treatment effects at each level of PASI response for brodalumab 210 mg vs comparators – Sensitivity analysis 2

Treatment	Risk ratio brodalumab 210 mg versus comparator, median (95% CrI)			
	PASI 50	PASI 75	PASI 90	PASI 100
Brodalumab 140mg				
Adalimumab 40mg Q2W				
Apremilast 20mg BID				
Apremilast 30mg BID				
Etanercept 50 mg / week				
Etanercept 100 mg / week				
Infliximab 5mg/kg				
Ixekizumab 80mg Q4W				
Ixekizumab 80mg Q2W				
Secukinumab 150mg				
Secukinumab 300mg				
Ustekinumab 45mg				
Ustekinumab 90mg				
Ustekinumab (in-label dose)				
Dimethyl Fumarate				
Fumaderm				
Methotrexate				
Acitretin				

Therapies other than the comparators of interest are shown in italics.
Risk ratios in bold indicate statistically significant differences.
[a] 95% credible interval does not span 1.
BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

B.2.9.4 Statistical assessment of heterogeneity

The trials included in the networks were largely similar with respect to baseline patient characteristics (see Appendix D.1.1.6.2). Table 31 summarises the tau heterogeneity parameter for base case and sensitivity analyses. Overall, there was low heterogeneity across the networks. The consistency of the results across the analyses (base case and scenarios) indicates that the outcomes of the NMA are robust.

Table 31 Tau values as a measure of precision for base case and sensitivity analyses

Analysis	Mean Tau	Tau SD	Median Tau	95% CrI	
Base Case	141.8	152.9	108.9	44.25	423
SA1	407.1	1600	113.4	32.37	2563
SA2	131.9	113.6	103.1	43.4	395.2
SA3	300.4	2210	106.4	43.18	614.7
SA4	201.9	802.4	102.4	36.41	641.4
SA5	160.2	310.4	105.1	41.97	544.1

CrI, credible interval; SA, sensisitivity analysis; SD, standard deviation.

Reference arm response rates are a useful proxy for both measured and unmeasured patient- and trial-level characteristics that may modify the observed treatment effect and introduce heterogeneity in meta-analysis. Substantial variation in placebo arm response rates could be a source of significant bias in cross-trial comparisons of treatment outcomes (124-126). An analysis was therefore undertaken to assess comparative efficacy using a model that includes adjustment for reference arm response rates. This adjustment has the potential to account for heterogeneity across trials in the network and improve the degree to which the NMA model fits the available data.

Analysis of goodness of fit (Table 32) shows that compared with the base-case analysis the adjusted model reduces unexplained heterogeneity and the variance of the random effect. However, although the adjusted model fit is better, the DIC approach penalises complexity and favours the unadjusted model overall. Data from the base-case analysis are therefore used in the economic model described in section B.3.

Table 32 Comparison of unadjusted and adjusted models by different diagnostic measures

Model diagnostic, mean (95% CrI)	Unadjusted model		Adjusted model	
	Random effects		Random effects	
Adjustment covariate	[redacted]		[redacted]	
Tau				
DIC				
Total residual deviance				

CrI, credible interval; DIC, Deviance Information Criterion.

B.2.9.5 Overview of NMA results

The NMA results have shown brodalumab 210 mg Q2W to be significantly more efficacious at inducing all levels of PASI response than adalimumab 40 mg Q2W, apremilast 30 mg BID, etanercept 50 mg weekly, infliximab 5 mg/kg, secukinumab 300 mg, ustekinumab (45 mg, 90 mg, and dosing as per label) and DMF, as well as all of the conventional systemic therapies in the network. The efficacy of brodalumab 210 mg Q2W was not significantly different from that of ixekizumab 80 mg Q2W.

The PASI responses predicted in the NMA for brodalumab 210 mg Q2W, ustekinumab and placebo were similar to those reported in the AMAGINE trials, suggesting that the direct and indirect evidence in the NMA are generally consistent. In addition, the results of the base-case analyses were robust to changes in the inclusion/exclusion criteria for the networks. The exclusion of evidence for other comparators, including unapproved doses of biologics, did not change the ranking of therapies in the base case. Similarly, the results of analyses excluding studies based on small sample size or because they included more severe patients (based on exposure to previous biologics or a high baseline PASI) were similar to the base case findings.

B.2.10 Adverse reactions

B.2.10.1 Safety results in AMAGINE-2 and AMAGINE-3

B.2.10.1.1 Exposure data

The safety analysis set included all randomised patients who received at least one dose of investigational product. For brodalumab, safety analyses were conducted based on constant dose (patients who received only brodalumab 140 mg Q2W or 210 mg Q2W during the study) and variable dose (patients who received brodalumab 210 mg Q2W after ustekinumab, who switched from 140 mg Q2W to 210 mg Q2W at re-randomisation or as rescue therapy, or who received mixed doses [140 mg Q4W or Q8W during the maintenance phase]).

The analysis presented here focusses on comparative safety among patients who received constant brodalumab 210 mg Q2W or ustekinumab throughout AMAGINE-2 and AMAGINE-3; data for other groups are described in the primary study publication (40), and are presented in Appendix F.

[redacted] Full details of exposure are shown in Appendix F, Table 93 (43, 44).

B.2.10.1.2 Summary of adverse events

Adverse events in the induction and maintenance phases of AMAGINE-2 and AMAGINE-3 are summarised in Table 33. The proportion of patients with an adverse event during the induction phase was higher in the brodalumab 210 mg Q2W group and the ustekinumab group than in the placebo group; adverse event rates were similar in the two active therapy groups (40).

The overall frequency of serious adverse events and events leading to discontinuation of the study or study medication was low, and was similar across randomised groups in both induction and maintenance phases (40).

B.2.10.1.3 Common adverse events

The most common adverse events in the induction phase of AMAGINE-2 and AMAGINE-3 were nasopharyngitis, upper respiratory tract infection, headache, and arthralgia (Table 34). With the exception of upper respiratory tract infection, these events were more frequent with brodalumab 210 mg Q2W than with placebo or ustekinumab in the AMAGINE-2 study; arthralgia was more frequent with brodalumab 210 mg Q2W in the AMAGINE-3 study (40).

Table 33 Summary of adverse events in AMAGINE-2 and AMAGINE-3 (SAS)

Induction phase (to week 12)	AMAGINE-2			AMAGINE-3		
Adverse event, n (%)	Placebo N= 309	Ustekinumab N= 300	Brodalumab, 210 mg Q2W N = 612	Placebo N= 313	Ustekinumab N= 313	Brodalumab 210 mg Q2W N = 622
Any	165 (53.4)	177 (59.0)	354 (57.8)	152 (48.6)	168 (53.7)	353 (56.8)
Serious [a]	8 (2.6)	4 (1.3)	6 (1.0)	3 (1.0)	2 (0.6)	9 (1.4)
Fatal [b]	0	0	1 (0.2)	0	0	0
Leading to discontinuation of study	0	2 (0.7)	6 (1.0)	2 (0.6)	1 (0.3)	5 (0.8)
Leading to discontinuation of drug	1 (0.3)	4 (1.3)	6 (1.0)	3 (1.0)	2 (0.6)	7 (1.1)
Grade 3, 4, or 5 [c]	10 (3.2)	11 (3.7)	25 (4.1)	8 (2.6)	8 (2.6)	23 (3.7)
Maintenance phase (to week 52)	**AMAGINE-2**			**AMAGINE-3**		
Adverse event, n (rate) [d]	Constant ustekinumab N = 300		Constant brodalumab, 210 mg Q2W N = 486 [e]	Constant ustekinumab N= 313		Constant brodalumab 210 mg Q2W N = 489 [e]
Exposure, patient-years	246.1		379.7	248.6		383.5
Any	1,017 (413.3)		1,531 (403.2)	935 (376.1)		1,522 (396.8)
Serious [a]	32 (13.0)		38 (10.0)	10 (4.0)		31 (8.1)
Fatal [e]	2 (0.8)		1 (0.3)	0		0
Leading to discontinuation of study	3 (1.2)		14 (3.7)	4 (1.6)		12 (3.1)
Leading to discontinuation of drug	10 (4.1)		18 (4.7)	7 (2.8)		15 (3.9)
Grade 3, 4, or 5 [c]	61 (24.8)		57 (15.0)	29 (11.7)		59 (15.4)

[a] A serious adverse event was defined as an event that was fatal or life threatening, led to inpatient hospitalisation or prolongation of existing hospitalisation, caused persistent or substantial disability or incapacity, caused a congenital anomaly or birth defect, or was considered by the investigator to be medically important.
[b] The fatal event was cerebral infarction (20 days after the last dose).
[c] The severity of adverse events was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
[d] Exposure-adjusted event rate per 100 patient-years.
[e] Constant brodalumab 210 mg Q2W group includes patients randomised to placebo and re-randomised to brodalumab 210 mg Q2W at week 12.
[f] Fatal events were: AMAGINE-2 cardiac arrest (constant 210 mg), cardiac arrest (ustekinumab), pancreatic carcinoma (ustekinumab); one additional fatal event occurred after the exposure period (completed suicide [placebo/210 mg; 27 days after last dose]); AMAGINE-3 cardiac arrest (140mg/210mg), accidental death (motor vehicle; 210 mg/140 mg Q2W); two additional fatal events occurred after the exposure period (histiocytosis haematophagic syndrome [140 mg/140 mg Q4W/210 mg rescue; 41 days after the last dose] and cardiomyopathy [210 mg /140 mg Q4W/210 mg rescue; 87 days after the last dose]).
Q2W, every 2 weeks; Q4W, every 4 weeks; SAS, safety analysis set.
Source: Lebwohl *et al.* 2015 (40).

B.2.10.1.4 Adverse events of interest

Adverse events of interest in AMAGINE-2 and AMAGINE-3 are shown in Tables 34 and 35 (40).

Induction phase

In the induction phase (Table 34), injection site reactions were the most common adverse event of interest; across the two studies, these occurred at a similar frequency in the brodalumab 210 mg Q2W, ustekinumab and placebo groups (the frequency was higher in the brodalumab 210 mg Q2W group than the other groups in AMAGINE-2, but lower in AMAGINE-3). *Candida* infections were the most common adverse event of interest in the brodalumab 210 mg Q2W group, and occurred more frequently in this group than in the ustekinumab and placebo groups; all of the infections were graded as mild or moderate, and none was systemic (40). In total, six serious infectious episodes were reported in the brodalumab 210 mg Q2W group, corresponding to 0.5% of patients, slightly higher than the placebo and ustekinumab groups (both 0.3% overall) (40).

Neutropaenia was more frequent in the brodalumab 210 mg Q2W and ustekinumab groups than in the placebo groups; cases of neutropenia were not associated with serious infections, and most cases were mild (absolute neutrophil count, > 1000/mm^3), transient, and reversible (40).

The rate of depression was similar across groups, and no cases of Crohn's disease or major adverse cardiac events were reported. There was one suicide attempt by a patient receiving brodalumab 210 mg Q2W in AMAGINE-2 (see section B.2.10.5) (40).

Maintenance phase

The frequency of adverse events of interest was generally similar in the maintenance phase (Table 35). The most common events were injection site reactions, which occurred at a similar frequency in the brodalumab 210 mg Q2W and ustekinumab groups, and *Candida* infections, which occurred more frequently with brodalumab 210 mg Q2W than with ustekinumab; as in the induction phase, all of the *Candida* infections were graded as mild or moderate, and none was systemic (40).

In total, three major adverse cardiac events were reported with constant brodalumab 210 mg Q2W (0.4 per 100 patient-years overall), and two with ustekinumab (0.4 per 100 patient-years overall). A total of seven cases of depression occurred in the brodalumab 210 mg Q2W groups (AMAGINE-2, 0.8 per 100 patient-years; AMAGINE-3, 1.0 per 100 patient-years), fewer than in the ustekinumab groups (ten; AMAGINE-2, 3.3 per 100 patient-years; AMAGINE-3, 0.8 per 100 patient-years) (40).

Suicidal ideation was experienced by three patients (ustekinumab, one [0.2 per 100 patient-years]; brodalumab 210 mg Q2W, two [0.3 per 100 patient-years]), and there were four suicide attempts in AMAGINE-2, one with ustekinumab and three with brodalumab 210 mg Q2W (these include three attempts by the same individual, one of which occurred during the induction phase). The rate of suicide attempts in the maintenance phase was 0.2 per 100 patient-years in the ustekinumab group, and 0.4 per 100 patient-years in the brodalumab group (Table 35). Suicide attempts and suicidal ideation are discussed in more detail in section B.2.10.5 (40).

B.2.10.1.5 Serious adverse events

A full listing of serious adverse events according to system organ class in the AMAGINE-2 and AMAGINE-3 induction and maintenance phases is shown in Appendix F, Table 98, Table 99, Table 100 and Table 101 (40).

In the induction phase, the overall incidence of serious adverse events across both studies was 1.8% with placebo, 1.0% with ustekinumab and 1.2% with brodalumab 210 mg Q2W. The most common serious adverse events were infections and infestations, which were slightly more common with brodalumab 210 mg Q2W (0.5% overall, vs 0.3% with each of placebo and ustekinumab; Table 33) (40).

The trend was similar in the maintenance phase, with serious adverse events reported by a similar proportion of patients treated with brodalumab 210 mg Q2W and ustekinumab overall (AMAGINE-2, 10.0 vs 13.0 events per 100 patient-years; AMAGINE-3, 8.1 vs 4.0; Table 33). Nervous system disorders were more common in patients treated with constant brodalumab 210 mg Q2W than in those receiving ustekinumab (eight vs zero events). The only individual nervous system disorders reported by more than one patient were syncope, which affected two patients in each study, and cerebrovascular accident, which affected one patient in each study (Appendix F, Table 100 and Table 101) (40).

Table 34 Adverse events of interest and common events in the induction phase of AMAGINE-2 and AMAGINE-3 (SAS)

Adverse event, n (%)	AMAGINE-2			AMAGINE-3		
	Placebo (N = 309)	Ustekinumab (N = 300)	Brodalumab 210 mg Q2W (N = 612)	Placebo (N = 313)	Ustekinumab (N = 313)	Brodalumab 210 mg Q2W (N = 622)
Adverse events of interest						
Crohn's disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depression	1 (0.3)	2 (0.7)	2 (0.3)	2 (0.6)	1 (0.3)	2 (0.3)
Suicide attempt	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Serious infectious episode	1 (0.3)	0 (0.0)	2 (0.3)	1 (0.3)	2 (0.6)	4 (0.6)
Appendicitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)
Urinary tract infection	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Localised infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Diverticulitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Meningitis cryptococcal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Peritonsilar abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Injection site reaction [a]	3 (1.0)	2 (0.7)	9 (1.5)	6 (1.9)	10 (3.2)	9 (1.4)
Adjudicated MACE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	0 (0.0)	2 (0.7)	1 (0.2)	0 (0.0)	1 (0.3)	7 (1.1)
Candida infections [b]	2 (0.6)	2 (0.7)	10 (1.6)	1 (0.3)	1 (0.3)	8 (1.3)
Common adverse events [c]						
Nasopharyngitis	14 (4.5)	18 (6.0)	45 (7.4)	22 (7.0)	16 (5.1)	31 (5.0)
Upper respiratory tract infection	23 (7.4)	20 (6.7)	30 (5.4)	17 (5.4)	16 (5.1)	33 (5.3)
Headache	9 (2.9)	12 (4.0)	31 (5.1)	14 (4.5)	11 (3.5)	21 (3.4)
Arthralgia	12 (3.9)	9 (3.0)	28 (4.6)	10 (3.2)	6 (1.9)	36 (5.8)

[a] Injection site reaction includes injections site pain, bruising, haemorrhage, discomfort, reaction, erythema, and uticaria, puncture site pain, and vessel puncture site bruise.
[b] *Candida* infections included all adverse events consistent with candidiasis infection.
[c] The most common adverse events are expressed according to the preferred term in the *Medical Dictionary for Regulatory Activities*, version 17.0 (AMAGINE-3) and 17.1 (AMAGINE-2), and were events that occurred in at least 5% of the patients in any treatment group during the induction phase.
MACE, major adverse cardiac events; Q2W, every 2 weeks; SAS, safety analysis set.
Source: Lebwohl *et al.* 2015 (40).

Table 35 Adverse events of interest in the maintenance phase of AMAGINE-2 and AMAGINE-3 (SAS)

	AMAGINE-2		AMAGINE-3	
Adverse event, n (rate) [a]	**Constant ustekinumab N = 300**	**Constant brodalumab, 210 mg Q2W N = 486 [b]**	**Constant ustekinumab N= 313**	**Constant brodalumab 210 mg Q2W N = 489 [b]**
Exposure, patient-years	246.1	379.7	248.6	383.5
Crohn's disease	0	0	0	0
Depression	8 (3.3)	3 (0.8)	2 (0.8)	4 (1.0)
Suicide attempt	1 (0.4)	3 (0.8) [f]	0	0
Suicidal ideation	0	1 (0.3)	1 (0.4)	1 (0.3)
Neutropenia	2 (0.8)	1 (0.3)	2 (0.8)	1 (0.3)
Candida infections [c]	10 (4.1)	16 (4.2)	4 (1.6)	27 (7.0)
Serious infectious episode				
Appendicitis	0	0	0	0
Cellulitis	0	0	1 (0.4)	2 (0.5)
Gastroenteritis	0	0	0	0
Pneumonia	0	1 (0.3)	0	0
Sepsis	0	1 (0.3)	0	0
Urinary tract infection	0	1 (0.3)	0	1 (0.3)
Other [d]	0	1 (0.3)	1 (0.4)	4 (1.0)
Injection site reaction [e]	9 (3.7)	24 (6.3)	18 (7.2)	22 (5.7)
Adjudicated MACE	2 (0.8)	2 (0.5)	0	1 (0.3)

[a] Exposure-adjusted event rate per 100 patient-years.
[b] Constant brodalumab 210 mg Q2W group includes patients randomised to placebo and re-randomised to brodalumab 210 mg Q2W at week 12.
[c] *Candida* infections included all adverse events consistent with candidiasis infection.
[d] Other serious infectious events include anal abscess, herpes zoster, perichondritis, tick-borne viral encephalitis, breast abscess, cellulitis of male external genital organ, cholecystitis infective, furuncle, groin abscess, meningitis cryptococcal, peritonsilar abscess, pyelonephritis acute, tubo-ovarian abscess, and viral tonsillitis.
[e] Injection site reaction includes injections site pain, bruising, haemorrhage, discomfort, reaction, erythema, uticaria, hematoma, mass, nodule, rash, and infection, puncture site pain, and vessel puncture site bruise
[f] Three events of suicide attempt occurred in one individual; the first event occurred during the 12 week induction period (Table 34).
MACE, major adverse cardiac events; Q2W, every 2 weeks; SAS, safety analysis set.
Source: Lebwohl *et al.* 2015 (40).

B.2.10.1.6 Deaths

In total, one death occurred during the induction phase, and five during the maintenance phase (including events in groups not receiving the treatments of interest; these are shown in Appendix F, Table 96 and Table 97). A further three deaths occurred after patients had stopped receiving treatment, [redacted] (see section B.2.10.3.1) (40, 49, 50). No causal relationship was found between brodalumab and suicidal ideation and behaviour (see section B.2.10.5).

In the induction phase, one patient in the AMAGINE-2 brodalumab 210 mg Q2W group died from stroke, 20 days after the last dose (40).

In the AMAGINE-2 maintenance phase, one patient who received brodalumab 210 mg Q2W continuously throughout the study died from cardiac arrest, and two patients in the ustekinumab group died, one each from cardiac arrest and pancreatic carcinoma. In AMAGINE-3 study, two patients who had received variable doses of brodalumab died, one from cardiac arrest and one from accidental death in a motor vehicle accident (40).

Three deaths occurred after exposure: in AMAGINE-2, one from completed suicide (in a patient who had received placebo followed by brodalumab 210 mg Q2W, 27 days after the last dose; see section B.2.10.5), and in the AMAGINE-3 study, one from haematophagic histiocytosis syndrome and one from cardiomyopathy (both patients had received variable doses of brodalumab) (40).

There was one additional suicide after week 52 during the open-label extension to AMAGINE-2 (in a patient who had received brodalumab 210 mg Q2W, 19 days after the last dose; see section B.2.10.5) (40).

B.2.10.1.7 Anti-drug antibodies

Occurrence of anti-brodalumab antibodies was infrequent and was not associated with a loss of efficacy or adverse events. No patient had neutralising antibodies. Non-neutralising anti-brodalumab antibodies were detected in four patients at baseline (40). Across all brodalumab groups, non-neutralising anti-brodalumab antibodies were detected during the period from baseline to week 52 in 28 brodalumab-treated patients (1.8%) in AMAGINE-2 and in 37 brodalumab-treated patients (2.3%) in AMAGINE-3 (40).

Among the patients who were randomly assigned to ustekinumab, samples from six patients after the initiation of ustekinumab therapy were positive for non-neutralising anti-brodalumab antibodies (40).

B.2.10.2 Safety results in AMAGINE-1

B.2.10.2.1 Exposure data

The safety analysis set included all randomised patients who received at least one dose of investigational product. For brodalumab, safety analyses were conducted based on constant dose (patients who received only brodalumab 140 mg Q2W or 210 mg Q2W during the

study) and variable dose (patients who received a combination of brodalumab 140 mg Q2W and 210 mg Q2W or were re-randomised to placebo in the withdrawal period).

The analysis presented here focusses on safety among patients who received placebo or brodalumab 210 mg Q2W in the induction period and constant brodalumab 210 mg Q2W to week 52; data for other groups are described in the primary study publication (41), and are presented in Appendix F.

Among the 649 patients who received at least one dose of brodalumab, the mean (SD) duration of exposure to brodalumab through week 52 was 291.2 (83.7) days (48).

B.2.10.2.2 Summary of adverse events

Adverse events in the induction and maintenance/withdrawal phases are summarised in Table 36. The proportion of patients with an adverse event during the induction phase was similar in the brodalumab 210 mg Q2W group and the placebo group (41). The overall frequency of serious adverse events and events leading to discontinuation of the study or study medication was low, and was similar across randomised groups (41).

B.2.10.2.3 Common adverse events

The most common adverse events in the induction phase of AMAGINE-1 were nasopharyngitis, upper respiratory tract infection and headache (Table 36); of these, upper respiratory tract infection and headache occurred more frequently in the brodalumab group than in the placebo group (41).

B.2.10.2.3 Adverse events of interest

The most common adverse event of interest was suspected *Candida* infection; all suspected *Candida* infections were mild to moderate (41).

B.2.10.2.4 Serious adverse events

In the induction phase, the overall incidence of serious adverse events was 1.4% with placebo and 1.8% with brodalumab 210 mg Q2W. [redacted] (40).

During the maintenance/withdrawal phase, the exposure-adjusted event rate of treatment-emergent serious adverse events for subjects exposed to brodalumab 210 mg Q2W was 9.9 events per 100 patient-years (the rate for all brodalumab exposure groups was 9.5 events per 100 patient-years) (41). [redacted]

Table 36 Summary of adverse events in AMAGINE-1 (SAS)

	Induction phase (to week 12)		Maintenance/withdrawal phase (to week 52)
	Placebo (n = 220)	Brodalumab 210 mg Q2W (n = 222)	Constant brodalumab 210 mg Q2W (n = 345, 271·8 patient-years)
Adverse events			
Any	112 (50·9)	131 (59·0)	1034 (380·4)
Serious	3 (1·4)	4 (1·8)	27 (9·9)
Fatal	0	0	3 (1·1)
Leading to discontinuation from study	3 (1·4)	2 (0·9)	9 (3·3)
Leading to discontinuation of study drug	3 (1·4)	2 (0·9)	10 (3·7)
Grade ≥ 3	9 (4·1)	15 (6·8)	55 (20·2)
Adverse events of interest			
Depression	1 (0·5)	1 (0·5)	2 (0·7)
Inflammatory bowel disease	0	0	0
Injection site reaction [a]	0	1 (0·5)	8 (2·9)
MACE	0	0	3 (1·1)
Neutropenia	0	0 (0·0)	1 (0·4)
Serious infectious episode	0	1 (0·5)	2 (1·7)
Suspected *Candida* infections [b]	3 (1·4)	5 (2·3)	11 (4·0)
Common adverse events (reported in ≥ 5% of patients in any treatment group to week 12)			
Nasopharyngitis	22 (10·0)	21 (9·5)	[redacted]
Upper respiratory tract infection	14 (6·4)	18 (8·1)	[redacted]
Headache	7 (3·2)	11 (5·0)	[redacted]

Values are n (%) to week 12 and n (exposure-adjusted event rate) to week 52.
MACE, major adverse cardiac event; Q2W, every 2 weeks; SAS, safety analysis set.
[a] Injection site reaction adverse events included reaction, erythema, haemorrhage, oedema, pain, extravasation, irritation, swelling and haematoma at the injection site.
[b] Suspected *Candida* infections included all adverse events consistent with *candidiasis* infection.
Source: Papp *et al*. 2016 (41), AMAGINE-1 CSR (48).

B.2.10.2.5 Deaths

A total of four patients died during AMAGINE-1, all during the maintenance/withdrawal phase: one sudden death, one illicit drug overdose (classified as suicide but ruled indeterminate by Columbia-Classification Algorithm for Suicide Assessment [C-CASA] adjudication [see section B.2.10.5.3]), one oesophageal varices haemorrhage and one cerebrovascular accident, all considered to be unrelated to brodalumab.

There was one additional suicide after week 52 during the open-label extension to AMAGINE-1 (in a patient who had received brodalumab 210 mg Q2W, 59 days after the last dose; see section B.2.10.5) (41).

B.2.10.2.6 Anti-drug antibodies

Occurrence of anti-brodalumab antibodies was infrequent and was not associated with a loss of efficacy or adverse events. No patient had neutralising antibodies. Non-neutralising anti-brodalumab antibodies were detected in four patients at baseline. Across all brodalumab

groups, non-neutralising anti-brodalumab antibodies were detected during the period from baseline to week 52 in 14 brodalumab-treated patients (2.2%) (40).

B.2.10.3 Safety results in long-term extension studies

B.2.10.3.1 Phase 3 open-label extension studies

The overall exposure to brodalumab to week 108/120 in the AMAGINE open-label extension studies was [redacted] patient-years for participants in AMAGINE-1, [redacted] patient-years for those in AMAGINE-2 and [redacted] patient-years for those in AMAGINE-3 (45, 49, 50). Adverse events in the open-label extension studies are summarised in Appendix F, Table 102, Table 103, and Table 104. [redacted]

B.2.10.3.2 Phase 2 open-label extension study

The phase 2 study (NCT00975637)) was a randomised, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of brodalumab in patients with moderate-to-severe plaque psoriasis (127). A total of 181 patients who received brodalumab (n = 148) or placebo (n = 33) in the phase 2 study entered the open-label extension study. At the data cut-off for the primary study publication, 148 (82%) patients had completed the 120-week visit (127). The 168-week analysis includes data for [redacted] of exposure to brodalumab, with the mean (SD) duration of exposure to brodalumab of [redacted] (128). Adverse events in the phase 2 open-label extension study are summarised in Appendix F, Table 105 and Table 106 (127, 128). The frequency of adverse events was consistent with the AMAGINE-2 and AMAGINE-3 safety data.

B.2.10.4 Overview of safety in relation to decision problem

In total, the safety analysis of the brodalumab psoriasis clinical trial programme includes [redacted] patient-years of exposure (the analysis of suicidal ideation and behaviour described in section B.2.10.5 is based on a total of 9,162 patient-years of data) (45, 49, 50, 128, 129). Overall, the most frequent adverse events were nasopharyngitis and upper respiratory tract infection – there was no consistent trend across studies towards these events being more common in the brodalumab 210 mg Q2W group than in the ustekinumab or placebo groups. Consistent with the known role of IL-17 in mediating in the immune response to fungal infections (130), *Candida* infections were slightly more common in the AMAGINE brodalumab 210 mg Q2W groups than in the ustekinumab and placebo groups; all of the infections were graded as mild or moderate, and none was systemic (22)(41).

During the randomised phase of AMAGINE-2 and AMAGINE-3, serious adverse events were reported by a similar proportion of patients treated with brodalumab 210 mg Q2W and ustekinumab; [redacted] (40, 41, 45, 49, 50, 128). Overall, the adverse event rates in the three AMAGINE trials appeared to be similar to those in the secukinumab and ixekizumab clinical programmes (71, 72).

A small proportion of patients in the AMAGINE trials experienced suicidal ideation and behaviour, and in total there were four completed suicides; however, no causal relationship was found between brodalumab and suicidal ideation and behaviour. Suicidal ideation and behaviour in the AMAGINE trial is described in detail in section B.2.10.5.

Conclusions

The safety profile of brodalumab has been directly compared with that of ustekinumab in AMAGINE-2 and AMAGINE-3. Safety data from these trials and the open-label extension phases suggest that the adverse event profiles of brodalumab and ustekinumab are comparable, [redacted]

B.2.10.5 Suicidal ideation and behaviour

Summary

- Brodalumab has several warnings and precautions for use, which are described in the SmPC (Appendix C). In particular, concerns exist over the risk of suicidal ideation and behaviour among patients with psoriasis, including those treated with brodalumab and other therapies.
- An independent analysis conducted by the FDA Division of Epidemiology found similar levels of suicidal ideation and behaviour events with brodalumab, apremilast, ixekizumab, and infliximab (131). The overall rate of suicidal behaviour for brodalumab was the same as that for ixekizumab, even though patients with a history of suicidal behaviour were excluded from the ixekizumab trials (131).
- A small proportion of patients in the AMAGINE trials experienced suicidal ideation and behaviour, and in total there were four completed suicides; however, no causal relationship was found between brodalumab and suicidal ideation and behaviour.
- Suicidal ideation and behaviour in psoriasis has been described in several previous studies, with patients with psoriasis having a significant increase in the likelihood of having clinical depression, anxiety and suicidal ideation, compared with people with no skin conditions.
- One key difference between the AMAGINE studies and clinical trials of some other biological therapies for psoriasis is that patients who might have an elevated risk of suicidal ideation and behaviour (due to history of depression, substance abuse, or prior history of suicidal behaviour) were not excluded from the AMAGINE studies.
    - The rate of suicidal ideation and behaviour in the AMAGINE studies was generally in keeping with that observed in other psoriasis trials with comparable patient populations.
    - The event rate for completed suicides in the brodalumab psoriasis program was 0.04 (95% CI: 0.01 to 0.11) per 100 patient-years, compared with an overall event rate of 0.03 (95% CI: 0.01 to 0.06) per 100 patient-years observed in external trials and registry data for other biological agents.
    - Depression and anxiety, measured with the HADS questionnaire, improved among patients treated with brodalumab in AMAGINE-1.
    - Most AMAGINE participants treated with brodalumab had no or minimal depression, measured with the Patient Health Questionnaire-8.

- There was no increase in neuropsychiatric events likely to precede suicidal behaviour in the AMAGINE studies.

- There is no plausible biological mechanism linking brodalumab with suicidal ideation and behaviour:
  - The results of pre-clinical studies showed no brodalumab-related neurobehavioral effects or effects on the central nervous system (CNS).
  - Pharmacokinetic and pharmacodynamic (PK/PD) investigations indicate that there is no evidence that a drug–drug or disease–drug interaction in patients taking antidepressants has the potential to play a causal role in suicidal ideation and behaviour.
  - There is no evidence of a relationship between brodalumab exposure levels and suicidal ideation and behaviour.
- In summary, despite the lack of restriction from the AMAGINE trials of patients who might have an elevated risk of suicidal ideation and behaviour, in contrast to the pivotal studies of some other therapies (109, 110), the data suggest that the risk of suicidal ideation and behaviour with brodalumab is no higher than that seen with other biological therapies.

B.2.10.5.2 Suicidal ideation and behaviour in the brodalumab trials

Brodalumab has several warnings and precautions for use, which are described in the SmPC (Appendix C). In particular, concerns exist over the risk of suicidal ideation and behaviour among patients with psoriasis, including those treated with brodalumab and other therapies. However, suicidal ideation and behaviour events were seen rarely in the brodalumab psoriasis programme, and no causal relationship was found between brodalumab and suicidal ideation and behaviour.

The study designs and open-label extensions meant that most patients were exposed to brodalumab 210 mg at some point. Limited exposure data for the placebo and ustekinumab groups, combined with the rarity of suicidal ideation and behaviour events, make it challenging to conduct meaningful comparisons with brodalumab. Overall, however, analysis of suicidal ideation and behaviour in the AMAGINE trials as described below suggests that the incidence of suicidal ideation and behaviour, which is common among people with psoriasis, is no higher with brodalumab than with other biological therapies.

B.2.10.5.3 Details of completed suicides in the brodalumab trials

There were four suicides in the brodalumab psoriasis programme, one of which was later adjudicated as indeterminate. Of these, two occurred during the 52-week ustekinumab-controlled period (including the indeterminate event) and two occurred during the uncontrolled open-label extension. All four suicides were by male patients with a history of depression and/or psychosocial stressors (financial or legal problems) (129).

B.2.10.5.4 Analysis of suicidal ideation and behaviour in the AMAGINE trials

An independent FDA analysis found similar levels of suicidal ideation and behaviour events with brodalumab, apremilast, ixekizumab and infliximab

In 2016 the FDA Division of Epidemiology conducted an analysis of suicidal ideation and behaviour in trials of biological therapies for psoriasis (131). The overall rate of suicidal

behaviour (attempted and completed) for brodalumab was the same as that observed in patients treated with ixekizumab (0.14 events per 100 patient-years), even though patients with a history of suicidal behaviour were excluded from the ixekizumab trials (131). Compared with brodalumab, higher rates of suicidal behaviour (attempts and completed combined) were found with infliximab (0.24 events per 100 patient-years) and apremilast (0.20 per 100 patient-years) (131).

Due to differences in methodology, comparison with older therapies is not straightforward. In particular, the "Prospective Assessment of Occurrence in Clinical Trials" guidance imposed in 2010 was not implemented in the development programmes for anti-TNF and anti-IL-12/23 therapies, so suicidal ideation and behaviour events may be under-reported in older studies (132).

People with psoriasis have an increased risk of experiencing suicidal ideation and behaviour

The risk of suicidal ideation and behaviour in psoriasis has been described in several studies (13, 24). These include a recent cross-sectional study conducted in 13 European countries, including the UK, which found that, compared with a control group with no skin conditions, dermatology outpatients with psoriasis (n = 626) were more likely to have (13):

- Clinical depression – adjusted Odds Ratio (aOR) 3.02, (95% CI: 1.86, 4.90)
- Anxiety – aOR 2.91, (95% CI: 2.01, 4.21)
- Suicidal ideation – aOR 1.94, (95% CI: 1.33, 2.82).

Among people with psoriasis in the European study, 17.3% had suicidal ideation, of which two-thirds (11.6% of people with psoriasis) was specifically due to their skin disease (13). In the UK, an analysis of the GPRD, including 149,998 patients with psoriasis, has estimated that each year more than 10,400 diagnoses of depression, 7,100 diagnoses of anxiety and 350 diagnoses of suicidality are attributable to psoriasis (24).

The AMAGINE studies did not exclude patients at elevated risk of suicidal ideation and behaviour

The inclusion criteria for the AMAGINE studies were broad, with fewer restrictions than some other clinical trials in psoriasis (see section B2.3.1.3). In particular, patients who might have an elevated risk of suicidal ideation and behaviour (due to history of depression, substance abuse, or prior history of suicidal behaviour) were not excluded. By contrast, the pivotal study of secukinumab, FEATURE (110), excluded patients with a history of drug or alcohol abuse, and the pivotal trials of ixekizumab, UNCOVER-2 and UNCOVER-3 (109), excluded patients with significant or severe uncontrolled neuropsychiatric disorders.

Suicidal ideation and behaviour event rates for brodalumab are consistent with other psoriasis therapies

For comparison with the brodalumab psoriasis programme, published data on other agents were reviewed; agents included were adalimumab, apremilast, brodalumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab, and ustekinumab. Overall, suicidal ideation and behaviour event rates for brodalumab are consistent with those for these other products:

- Completed suicides reported in the US Food and Drugs Administration (FDA) 120-day safety update on the brodalumab psoriasis programme were 4 out of 9,162 patient-years. This represents a rate of 0.04 per 100 patient-years, compared with 0.05 per 100 patient-years in the initial licence application (including one event reported as intentional overdose adjudicated by the blinded adjudication committee as indeterminate).
- Based on the 120-day safety update, the event rate for completed suicides in the brodalumab psoriasis program is 0.04 (95% CI: 0.01 to 0.11) per 100 patient-years, compared with an event rate of 0.03 (95% CI: 0.01 to 0.06) per 100 patient-years observed in external trials and registry data for other agents (133).
- Since suicide is rare, rates in psoriasis clinical programmes vary greatly. Some programmes had no cases of suicide while in one programme (apremilast) the rate was estimated at 0.23 per 100 patient-years in the 16-week controlled part of the trial.

The rate of suicidal ideation and behaviour in the AMAGINE studies was generally low, but was higher in participants with a prior history of depression or suicidality

Following discussions with regulators, in March 2014 the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) was added to the AMAGINE-1, AMAGINE-2 and AMAGINE-3 trial protocols (45, 49, 50).

An analysis of the AMAGINE trials was performed by the FDA Division of Biometrics, which found that brodalumab-treated patients with baseline depression or suicidality had a 7-fold and 12–18-fold increase, respectively, in rates of suicidal ideation and behaviour, compared with patients without such histories (134). No comparable analysis of other biological therapies has been performed, and it is important to evaluate patients' history of depression and suicidality prior to initiating treatment with any biological therapy.

[1] These percentages do not add up to 100% due to missing data for approximately 1% of patients in each study.

Most AMAGINE participants treated with brodalumab had no or minimal depression, measured with the Patient Health Questionnaire-8

[redacted]

There was no increase in neuropsychiatric events likely to precede suicidal behaviour

An increased frequency of neuropsychiatric adverse events, including depression and/or anxiety, which are known to be associated with suicidal ideation and behaviour, might be anticipated to precede suicidal events. However, no increase in neuropsychiatric adverse events was observed in patients treated with brodalumab. This was investigated using the nervous systems disorders MedDRA system organ class (SOC), the psychiatric disorders SOC and the depression Standardised MedDRA Query (SMQ), using data from the phase 2 study and the three AMAGINE trials (67).

From baseline to week 52, the rate of nervous system disorder adverse events was 23.5 per 100 patient-years among patients treated with brodalumab (all doses), compared with 24.0 per 100 patient-years in the AMAGINE ustekinumab groups. Up to the end of the studies, the follow-up adjusted rates did not increase in the brodalumab long-term pool (Table 37) indicating no evidence of increasing rates of nervous system disorders with increasing patient-years of exposure to brodalumab. Similar results were seen for psychiatric disorders and depression, with no imbalance seen between brodalumab and ustekinumab, and no increase in event rates over time (Table 37).

Table 37 Follow-up observation time-adjusted rates of nervous system disorder adverse events through Week 52 and end of study

	52-week pool		Long-term pool
	Ustekinumab N = 613 504 patient-years	All brodalumab doses N = 4019 3548 patient-years	All brodalumab doses N = 4464 9174 patient-years)
Nervous system disorders SOC, n (r)	121 (24.0)	833 (23.5)	1402 (15.3)
Psychiatric disorders SOC, n (r)	47 (9.3)	269 (7.6)	571 (6.2)
Depression SMQ, n (r)	21 (4.2)	92 (2.6)	221 (2.4)

N = patients in the phase 2 study, AMAGINE-1, AMAGINE-2, and AMAGINE-3 with ≥ 1 dose of investigational product.
n = number of adverse events; r = follow-up observation time-adjusted event rate per 100 patient-years of follow-up.
Analysis used CTCAE v. 4.0 or 4.03, MedDRA v. 17.1 (52-week pool), and MedDRA v. 18.1 (long-term pool).
Multiple occurrences of the same event for a patient are counted as multiple events.
SMQ, Standardised MedDRA Query; SOC, system organ class.
Source: Valeant FDA briefing document (67).

There is no plausible biological mechanism linking brodalumab with suicidal ideation and behaviour

An analysis conducted by Valeant Pharmaceuticals as part of the FDA regulatory process concluded that a biological linkage between brodalumab and suicidal ideation and behaviour events appears unlikely (67):

- In pre-clinical studies in cynomolgus monkeys, there were no brodalumab-related neurobehavioral effects or effects on the central nervous system (CNS) as assessed clinically and through anatomical pathology endpoints. In addition, there were no clinical observations or effects that supported a brodalumab-related change in body weight, food consumption or heart rate, all of which have been associated with depression in animals.
- A number of studies have investigated a potential correlation between IL-17 and various forms of depression and other psychiatric conditions; however, no causal relationship has been established between changes in serum levels of pro-inflammatory cytokines and suicidal ideation or behaviour.
- Gene expression studies have found IL-17RA to be expressed across many regions of the human brain, at levels which are lower than in neutrophils and increase after brain injury. It is unclear whether there is any physiological role of IL-17RA in the brain in the absence of ischaemic, infectious, or direct autoimmune attack on the CNS.
- Based on pre-clinical studies in rodents, the fraction of brodalumab crossing the blood–brain barrier is expected to be very low, at approximately 0.1% of serum concentration. Therefore, brodalumab would not be expected to inhibit IL-17RA signalling in the CNS more than perhaps briefly after dosing when serum concentrations are at their highest.
- In AMAGINE-1, there was a brodalumab dose-dependent increase in serum IL-17A was observed that can be attributed to a dose-dependent blockade of the receptor-mediated clearance of IL-17A. However, at the top dose of 210 mg Q2W, the post-treatment IL-17A levels remained within the range of baseline IL-17A levels for the majority (> 75%) of patients. Given the generally modest elevation of IL-17A relative to the baseline range for the psoriasis population and the expected low partitioning of IL-17A across the blood–brain barrier, the increased levels of IL-17A in serum are not expected to exert effects within the CNS.
- PK/PD investigations indicate that there is no evidence that a drug–drug or disease–drug interaction in patients taking antidepressants has the potential to play a causal role in suicidal ideation and behaviour. Moreover, there is no evidence of a relationship between brodalumab exposure levels and suicidal ideation and behaviour.

Furthermore, a recent independent review of the safety of IL-17 agents including brodalumab has not found any evidence of a causal association or a pathogenic mechanism linking brodalumab treatment to the risk of suicidal behaviour (135).

In summary, despite the lack of restriction from the AMAGINE trials of patients who might have an elevated risk of suicidal ideation and behaviour, in contrast to the pivotal studies of some other therapies (109, 110), the data suggest that the risk of suicidal ideation and behaviour during treatment of moderate-to-severe psoriasis with brodalumab is no higher than that seen with other biological therapies.

B.2.11 Ongoing studies

There are no completed or ongoing studies that will provide additional evidence within the next 12 months.

B.2.12 Innovation

The cost-effectiveness analysis described in section B.3 models the benefits of brodalumab based on PASI response rates in the AMAGINE trials. In addition to the utility gains associated with improvement in PASI score, the AMAGINE trials have demonstrated a number of benefits of brodalumab that may not be included in the incremental cost-effectiveness ratio: brodalumab has the potential to deliver complete skin clearance for many patients; is efficacious in the treatment of nail and scalp psoriasis; is associated with rapid responses while requiring fewer induction doses than the anti-TNF therapies; delivers sustained responses, even after treatment interruption; and provides clinicians and patients with an alternative choice within the IL-17 class of biological therapies.

Brodalumab has the potential to deliver complete skin clearance for many patients
PASI 75 response is used in NICE guidance and BAD guidelines as a measure of treatment success in psoriasis (2, 29). However, many patients achieving PASI 75 report that psoriasis still affects their lives (36), and improvements in patient-reported symptom burden and HRQoL have been shown to be greater with PASI 100 than with PASI 75 (35, 36). PASI 100, representing a complete clearance of psoriasis symptoms, is the ultimate treatment goal for patients (35).

Across the three AMAGINE studies, more than one in three patients achieved PASI 100 within 12 weeks with brodalumab 210 mg Q2W (see sections B.2.6.2.2 and B.2.6.3.2), significantly more than with ustekinumab (in AMAGINE-2 and AMAGINE-3). At 52 weeks in AMAGINE-2 and AMAGINE-3, more than half of patients treated with continuous brodalumab 210 mg Q2W had PASI 100, compared with fewer than one-third in the ustekinumab group (see section B.2.6.2.3).

In delivering complete skin clearance for more than half of patients, brodalumab represents a step-change in the management of moderate-to-severe psoriasis. PASI 100 is included as a category in the utility value calculation in the economic model (see section B.3). However, the long-term HRQoL benefits of complete clearance of psoriasis symptoms may not be fully captured within the quality-adjusted life-year (QALY) calculation. In addition, compared with patients with lower levels of treatment response, the HRQoL benefits associated with achieving PASI 100 may mean that these patients are less likely to require additional dermatologist visits or to switch therapies. The high proportion of patients reaching PASI 100

with brodalumab may therefore reduce healthcare costs; this potential benefit is not fully captured within the economic model.

Brodalumab is efficacious in the treatment of nail and scalp psoriasis

Scalp psoriasis occurs in 50% to 80% of patients with psoriasis. Scalp psoriasis may be associated with pruritus, pain, and social stigma, and can severely impact quality of life due to external exposure (136). In addition, up to 50% of patients with plaque psoriasis have concurrent nail psoriasis, with an estimated lifetime incidence of 80% to 90% (137). Nail involvement may place a significant burden on patients as a result of functional impairment of manual dexterity, pain, and psychosocial embarrassment (138). Historically, the nails and the scalp are among the most problematic areas to treat (139).

In AMAGINE-1, most patients treated with brodalumab 210 mg Q2W had a 75% improvement in scalp symptoms, measured with the PSSI (see section B.2.6.3.2). Similarly, in AMAGINE-2 and AMAGINE-3, brodalumab 210 mg Q2W was associated with a larger decrease in nail psoriasis, measured with the NAPSI, than ustekinumab (see section B.2.6.2.2). However, scalp and nail symptoms are poorly represented in the PASI (139) and may not be adequately captured by the EQ-5D. Therefore, these benefits of brodalumab may not be fully included in the QALY calculation.

Response to brodalumab treatment is rapid, with fewer induction doses required than some other biological therapies

In AMAGINE-2 and AMAGINE-3, the effects of brodalumab 210 mg Q2W were observed as early as 2 weeks following treatment, with a median time to PASI 75 response of 4 weeks, compared with 8 weeks for the active comparator ustekinumab ($p < 0.001$; see section B.2.6.2.2) (40). In addition to this rapid treatment response, brodalumab requires fewer doses during the induction phase than some other biological therapies, notably adalimumab and etanercept, which require 10 and 12 induction doses, respectively. Therefore, brodalumab may limit the cost of early treatment failure and the associated budget uncertainty. In addition, in a discrete choice experiment, patients with psoriasis were found to show a preference for treatments with a faster onset of action (140); consequently, the benefits to patients of the rapid onset of efficacy with brodalumab may not be captured in the QALY calculation.

Use of brodalumab is associated with a sustained response to treatment, even if therapy is interrupted

A limitation of current biological therapies for moderate-to-severe psoriasis is that many patients discontinue treatment with biological therapies due to a loss of response over time or adverse effects (32-34). In the BADBIR registry, 23% of patients being treated with a first biologic discontinued within 1 year, and 47% had done so by year 3. Although ustekinumab was associated with lower discontinuation rates than anti-TNF therapies (potentially due to a lack of more efficacious approved therapies at the time this analysis was conducted), 25% of patients receiving ustekinumab had discontinued treatment within 3 years (33).

Data from the AMAGINE-2 and AMAGINE-3 trials suggest that brodalumab compares favourably to ustekinumab with regard to sustained responses to treatment. During the AMAGINE-2 and AMAGINE-3 maintenance phase, fewer patients receiving brodalumab

210 mg Q2W had an inadequate response at any treatment visit, compared with the ustekinumab group (see section B.2.6.2.3) (40). In addition, PASI 75 and PASI 90 response rates were maintained to week 52, with a slight increase in PASI 100 response rate (40).

One reason that patients in clinical practice may need to discontinue their treatment and switch to another therapy is loss of response after treatment interruption due to infection, surgery or pregnancy (141). The efficacy of brodalumab after treatment interruption was tested in AMAGINE-1, which found a high rate of response after re-treatment (see section B.2.6.3.4) (41).

Together, the results of the AMAGINE trials suggest that brodalumab is likely to provide long-term, sustained improvement in moderate-to-severe psoriasis. Compared with other biologics, patients in clinical practice may be more likely to remain on brodalumab therapy, and even if treatment is paused, may be less likely to have issues with their treatment or need to switch therapy after resuming. Consequently, brodalumab would be expected to reduce the number of unscheduled clinic visits (each dermatology outpatient visit is estimated to cost £96; see section B.3.5.1 (142)) and the need for patient re-assessment and treatment switching.

The economic model conservatively assumes equal discontinuation rates for all therapies in the base-case analysis (see section B.3.3.2). Consequently, the benefits of the expected low discontinuation rate with brodalumab may not be captured in the QALY calculation.

With a different mechanism of action, brodalumab provides an alternative choice within the IL-17 class

The IL-17 pathway plays a central role in psoriasis pathogenesis and is a critical therapeutic target (25). The recently developed agents secukinumab and ixekizumab target the IL-17A ligand (25). By contrast, brodalumab is a human monoclonal antibody that targets the IL-17-receptor A (IL-17RA) (37). The first IL-17 inhibitor to act on the IL-17 receptor on keratinocytes and immune cells, brodalumab blocks the biological activity of the pro-inflammatory cytokines IL-17A, IL-17F, IL-17A/F heterodimer and IL-25, inhibiting the inflammation and clinical symptoms associated with psoriasis (25). With a mechanism of action different from IL-17A inhibitors, brodalumab provides clinicians and patients with an alternative choice within this newest class of biological therapies for the treatment of moderate-to-severe psoriasis in adults.

B.2.13 Interpretation of clinical effectiveness and safety evidence

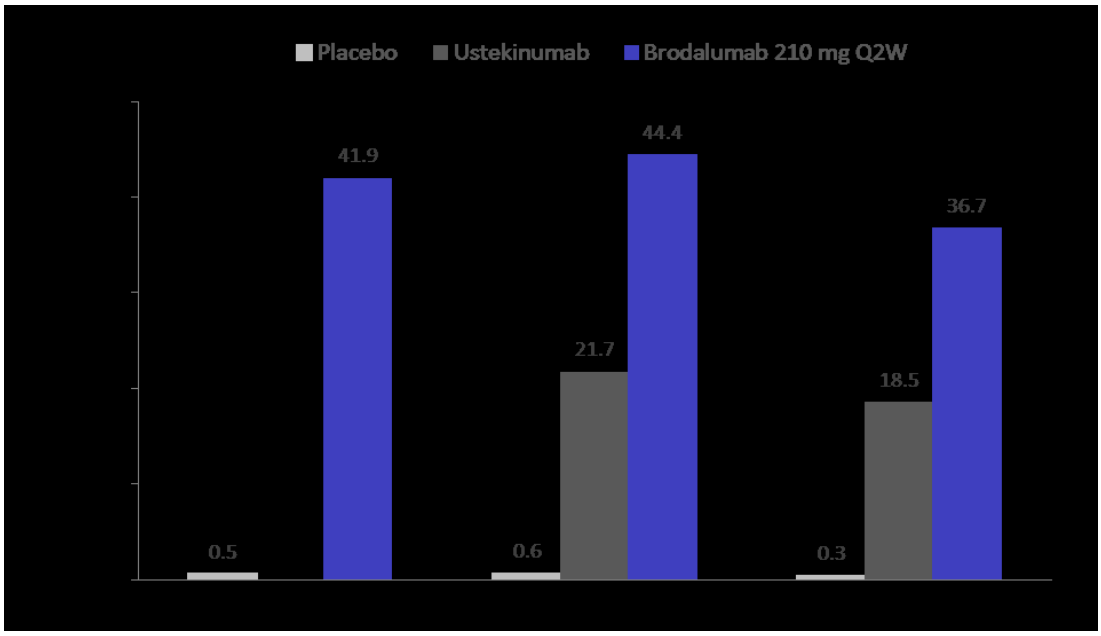
B.2.13.1 Principal findings from the AMAGINE clinical studies

The efficacy of brodalumab 210 mg Q2W for the treatment of moderate-to-severe psoriasis in adults was demonstrated in three phase 3 trials: AMAGINE-1, AMAGINE-2 and AMAGINE-3. Brodalumab demonstrated rapid and sustained improvements in psoriasis symptoms and HRQoL compared with placebo and the active comparator ustekinumab, with a comparable safety profile.

The primary endpoints were met in all three AMAGINE studies, with significantly greater sPGA and PASI response rates with brodalumab 210 mg Q2W than with placebo or ustekinumab (AMAGINE-2 and AMAGINE-3) at week 12 (40, 41). Response rates were maintained to week 52 and during the open-label extension phase (40, 41, 45, 49, 50).

Overall, clinical responses were highly consistent among the phase 3 trials, with 36.7–44.4% of patients treated with brodalumab 210 mg Q2W achieving PASI 100 (completely clear skin) at 12 weeks, a significantly higher response rate than in the ustekinumab and placebo groups (Figure 28) (40, 41).

Figure 28 Proportion of patients with PASI 100 response at week 12 in AMAGINE trials (FAS, NRI)



Missing data were imputed as nonresponses (see section B.2.4.4).
* $p < 0.001$ vs ustekinumab. † $p < 0.001$ vs placebo.
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index.
Source: Lebwohl *et al.* 2015 (42); Papp *et al.* 2016 (41).

Responses to brodalumab 210 mg Q2W in the AMAGINE trials were rapid and sustained. In AMAGINE-2 and AMAGINE-3, the median time to PASI 75 response was 4 weeks, compared with 8 weeks for the active comparator ustekinumab ($p < 0.001$; see section B.2.6.2.2) (40). During the maintenance phase, PASI 75 and PASI 90 response rates were sustained to week 52, and the majority of patients (53–56%) treated with constant brodalumab 210 mg Q2W achieved PASI 100 at week 52, while fewer patients in the brodalumab 210 mg Q2W group than in the ustekinumab group had an inadequate response at any treatment visit (see section B.2.6.2.3) (40).

In addition to efficacy in patients receiving continuous therapy, the AMAGINE trials demonstrated the efficacy of brodalumab 210 mg Q2W administered after a prior biological therapy (ustekinumab) had failed to generate an adequate response, or after withdrawal of therapy. In AMAGINE-2 and AMAGINE-3, 20% of patients randomised to ustekinumab switched therapies due to an inadequate response at week 16. Of these, most patients

(86%) achieved a PASI 75 response by week 52, and 42% achieved completely clear skin (PASI 100) at week 52 (see section B.2.6.2.3) (40). In AMAGINE-1, a total of 84 patients who had an sPGA response (0 or 1) at week 12 were re-randomised to placebo; of these, 79 experienced a return of disease (sPGA ≥ 3) during the withdrawal phase. Re-treatment with brodalumab was effective in almost all patients, with a median time to recapture sPGA response of 4.1 weeks. Therefore, compared with other biologics, patients in clinical practice may be more likely to remain on brodalumab therapy, and even if treatment is paused, may be less likely to have issues with their treatment or need to switch therapy after resuming.

In addition to overall clearance of psoriasis, measured as PASI and sPGA scores, brodalumab was associated with improvements in psoriasis of the scalp and nails, both of which can impact patients' HRQoL, and which are historically problematic areas to treat (139). Most patients treated with brodalumab 210 mg Q2W had a 75% improvement in scalp symptoms, measured with the PSSI in AMAGINE-1 (see section B.2.6.3.2). Similarly, the improvement in nail psoriasis, measured with the NAPSI in AMAGINE-2 and AMAGINE-3, was greater with brodalumab 210 mg Q2W than ustekinumab (see section B.2.6.2.2).

Patients treated with brodalumab in the AMAGINE trials had significant improvements in HRQoL. Compared with ustekinumab, treatment with brodalumab 210 mg Q2W was associated with an increased likelihood of psoriasis no longer having an effect on a patient's life, as assessed with the DLQI, compared with ustekinumab. In addition, evidence from AMAGINE-1 demonstrated statistically significant reductions in depression and anxiety, assessed with the HADS questionnaire, as well as statistically significant and clinically relevant improvements in EQ-5D utility (which increased from 0.60 at baseline to 0.85 at week 12; see section B.2.6.3.5).

High PASI 75, PASI 90 and PASI 100 response rates were seen with brodalumab 210 mg Q2W in all patient subgroups, including subgroups defined by disease severity and previous use of systemic therapy and phototherapy (see section B.2.7). Brodalumab PASI response rates were similar for patients with and without prior use of biological therapies.

In an NMA of PASI response rates (see section B.2.9), brodalumab 210 mg Q2W was found to be significantly more efficacious than adalimumab 40 mg Q2W, apremilast 30 mg BID, etanercept 50 mg weekly, infliximab 5 mg/kg, secukinumab 300 mg, ustekinumab (45 mg, 90 mg, and dosing as per label) and DMF. The efficacy of brodalumab 210 mg Q2W was not significantly different from that of ixekizumab 80 mg Q2W.

In all three AMAGINE trials, the frequency of serious adverse events and events leading to discontinuation of the study or study medication was low, and was similar across randomised groups in both induction and maintenance phases. In the active-controlled AMAGINE-2 and AMAGINE-3 trials, the overall safety profile of brodalumab 210 mg Q2W was comparable to that of ustekinumab. Injection site reactions were the most common adverse event of interest; across the three studies, these occurred at a similar frequency in the brodalumab 210 mg Q2W, ustekinumab and placebo groups. *Candida* infections were slightly more common in the AMAGINE brodalumab 210 mg Q2W groups than in the ustekinumab and placebo groups; all infections were graded as mild or moderate, and none

was systemic (40, 41). [redacted]

Several patients in the AMAGINE trials experienced suicidal ideation, and in total there were four completed suicides; however, no causal relationship was found between brodalumab and suicidal ideation and behaviour. An independent analysis of suicidal ideation and behaviour in the AMAGINE trials by the FDA Division of Epidemiology concluded that the incidence of suicidal ideation and behaviour, which is common among people with psoriasis, is no higher with brodalumab than with other biological therapies.

B.2.13.2 Strengths and limitation of the clinical evidence base for brodalumab

Study design

The clinical evidence provided by the three AMAGINE trials demonstrates the efficacy and safety of brodalumab in the treatment of moderate-to-severe psoriasis. All of the AMAGINE trials met their primary endpoints, and demonstrated rapid and sustained improvements in psoriasis symptoms and HRQoL with brodalumab compared with placebo and the active comparator ustekinumab.

A strength of the brodalumab clinical programme is that the two identical AMAGINE-2 and AMAGINE-3 trials included a 52-week treatment period with an active comparator, and that the primary endpoint in both trials was the proportion of patients achieving PASI 100, the most appropriate patient-relevant endpoint for distinguishing between highly effective therapies. This provides a robust assessment of the sustained high-level response to brodalumab therapy.

The active comparator in AMAGINE-2 and AMAGINE-3 was ustekinumab, which is approved for the treatment of moderate-to-severe psoriasis in England and Wales as well as in many other countries; before the assessment of secukinumab in 2015, ustekinumab was the most efficacious therapy recommended by NICE for patients with severe disease (PASI ≥ 10 and DLQI > 10) (70, 71). Ustekinumab has been shown to be an efficacious therapy for the induction and maintenance of clinical response (117, 118, 143). In the BADBIR registry, ustekinumab was associated with a greater likelihood of persistence with treatment than the anti-TNF therapies adalimumab, infliximab and etanercept (33). Patients randomised to ustekinumab were switched to brodalumab 210 mg Q2W rescue therapy if they had an inadequate response at week 16. This approach reduced the amount of data on ustekinumab treatment (20% of patients randomised to ustekinumab switched to brodalumab), but allowed evaluation of the efficacy of brodalumab 210 mg Q2W treatment following inadequate response to ustekinumab (see section B.2.6.2.3).

As for other clinical trials in psoriasis, a limitation of the AMAGINE studies is the lack of direct comparisons with active comparators other than ustekinumab. This limitation has been addressed by conducting an NMA to allow indirect comparisons with all of the comparators in the NICE decision problem.

A strength of the AMAGINE-1 trial is the inclusion of a withdrawal and re-treatment phase. In clinical practice, patients may interrupt their biological psoriasis therapy for reasons including infection, surgery, pregnancy or holiday. However, not all patients regain their former response level after treatment is resumed. AMAGINE-1 allowed the efficacy of brodalumab re-treatment after a loss of treatment response (following re-randomisation to placebo) to be tested, and demonstrated that almost all patients regained treatment response after 12 weeks of re-treatment (see section B.2.6.3.4).

Relevance of outcomes

The main efficacy outcome assessed in the AMAGINE studies was the PASI score, a measure of psoriasis disease severity based on a calculation of plaque qualities, including induration, erythema, and desquamation, and the area involved with psoriasis (57). PASI 75 is often used a clinically meaningful endpoint that represents an adequate response to treatment (2, 29, 57). However, many patients achieving PASI 75 report that psoriasis still affects their lives (36), and improvements in patient-reported symptom burden and HRQoL have been shown to be greater with PASI 100 than with PASI 75 (35, 36). With the high levels of efficacy demonstrated by recent therapies, PASI 100 may be the most appropriate patient-relevant endpoint (35).

In addition to PASI scores, NICE guidelines recommend use of DLQI scores to assess the efficacy of systemic and biologic interventions for psoriasis (1). The DLQI score (0 to 30) is calculated from ten questions based on skin disease symptoms and impact on HRQoL (61). A 5-point improvement from baseline at a specific visit is defined as a clinically meaningful change (62), while a DLQI score of 0 or 1 indicates that the disease has no effect at all on a patient's life (63). Mirroring the PASI 100 endpoint – completely clear skin – a DLQI score of 0 or 1 – no effect at all – is therefore a highly patient-relevant therapeutic goal in the treatment of psoriasis.

Other outcomes included sPGA and PSI; in addition, HADS and EQ-5D were included in AMAGINE-1. All of these are widely used, validated endpoints (see section B.2.3.1.5) (57, 60).

Trial population

The AMAGINE-2 and AMAGINE-3 trials were conducted at 284 sites in Australia, Canada, Europe, and the USA, and the results achieved in this broad population are expected to be applicable to patients in England.

The AMAGINE studies were designed to include a typical moderate-severe psoriasis population with few restrictions. Compared with the BADBIR registry population, the mean age at baseline was similar in the AMAGINE studies, the mean duration of disease was slightly lower (18−20 vs 23 years), and there was a slightly higher proportion of men (69−73 vs 59%) (40, 41, 66). Mean bodyweight and mean body mass index in the AMAGINE trials were similar to those in the BADBIR registry population (90–91 vs 90 kg and 30–31 vs 31 kg/m^2, respectively) (40, 41, 66). Patients with psoriatic arthritis were not excluded: 19% of

participants in AMAGINE-2 and AMAGINE-3, and 27% of those in AMAGINE-1, had psoriatic arthritis, a similar proportion to the BADBIR population (23%) (40, 41, 66).

Patients with known cardiovascular disease (other than a myocardial infarction or unstable angina in the previous 12 months) were not excluded from the AMAGINE studies, yielding a realistic population. Furthermore, in contrast to some previous psoriasis development programmes (109, 110), there were no specific exclusion criteria for psychiatric disorders or substance abuse. Therefore, patients with depression, substance abuse, or prior history of suicidal behaviour could enter the studies (40). As depression is common in patients with psoriasis (22.1% of those in the BADBIR registry had depression (66)), the AMAGINE population is likely to be more realistic than some previous studies.

Patients included in the AMAGINE studies could have received prior psoriasis therapy, including previous biological therapy: more than 25% of AMAGINE participants had received prior biological therapy (40, 41). Prior use of ustekinumab was prohibited in AMAGINE-2 and AMAGINE-3 because it was the active comparator in those studies (40).

B.2.13.3 Life expectancy of people with psoriasis

There is evidence that people in England with severe psoriasis may have a reduced life expectancy compared with people without psoriasis, primarily as a result of comorbidities including cardiovascular disease and cancer (144). In a UK GPRD study, male and female patients with moderate-to-severe psoriasis died 3.5 and 4.4 years younger, respectively, than patients without psoriasis ($p < 0.001$), and a significant increase in mortality risk was found after adjustment for other risk factors (hazard ratio, 1.42; 95% CI, 1.25–1.62) (15). This hazard ratio for increased mortality is included in the economic model described in section B.3.

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

B.2.13.4 Estimated number of patients eligible for treatment with brodalumab in England

An estimate of the number of patients eligible for treatment with brodalumab in England is shown in Table 38. Based on a prevalence in adults of 3.013%, the estimated number of patients eligible to receive biological therapy is 17,300 (2, 3, 145).

Table 38 Estimated number of patients with psoriasis in England eligible for treatment with brodalumab

Population	% of previous row	Number of people
Total adult population of England (age ≥ 20 years) [a]	–	42,857,200
Prevalence of psoriasis [b]	3.013	1,291,274
People with plaque psoriasis [c]	90	1,162,147
People eligible for biological treatment [d]	2.55	29,635

[a] 2018 population projection by the Office for National Statistics, ages 20 years and over (146).
[b] 3.013% is 2018 forecast in Springate *et al.* 2017 (4).
[c] NICE Clinical Guideline 153 (2).
[d] NICE Resource impact report: Ixekizumab for treating moderate-to-severe plaque psoriasis (TA442) (145).

B.3 Cost effectiveness

Summary

- A pharmaco-economic model was developed based around induction and maintenance periods as used in clinical practice.
    - Response to treatment and outcomes are modelled based on PASI response thresholds. Utility values were calculated from AMAGINE-1 EQ-5D data. Adverse event rates were based on the literature.
    - Cost inputs comprise biological therapy acquisition and administration costs, monitoring costs, and costs associated with best supportive care (BSC).
    - For brodalumab, the acquisition cost includes a confidential patient access scheme (PAS) discount.
    - The perspective of this analysis was that of the England and Wales NHS and Personal Social Services, with a 40-year model duration.
    - The model was used to perform a cost-effectiveness analysis comparing brodalumab with the comparators in the NICE scope as first-line therapies for the treatment of eligible patients who have failed to respond to prior conventional systemic therapies; in total, three lines of therapy were modelled, followed by BSC.
- The cost-effectiveness analysis results demonstrate that, compared with DMF, apremilast, etanercept, adalimumab, ustekinumab, secukinumab and infliximab, brodalumab 210 mg Q2W is associated with more quality-adjusted life years (QALYs).
    - In pairwise analyses, the ICERs for brodalumab versus DMF, apremilast, and etanercept were all less than £15,000 per QALY, while brodalumab dominated adalimumab, ustekinumab, secukinumab and infliximab (providing more QALYs at a lower cost).
    - In fully incremental analysis, apremilast, etanercept, adalimumab, ustekinumab, secukinumab and infliximab were dominated or extendedly dominated.
    - Ixekizumab was associated with slightly more QALYs than brodalumab, with an incremental ICER of £894,010 per QALY.
    - Probabilistic sensitivity analysis shows that at a willingness-to-pay threshold of £20,000 per QALY brodalumab has the highest probability of being cost-effective (96.2%).
    - The model results were found to be generally robust in deterministic sensitivity analysis, with the acquisition costs of psoriasis therapies, the annual cost of BSC and the annual discontinuation rate having the greatest impact on the results.
- Strengths of the economic analysis include the use of QALYs based on directly-elicited utility values as the primary outcome, and the use of PASI 100, representing complete skin clearance, as a distinct response level.
- The results of this analysis are expected to be applicable to clinical practice in England and Wales: the main source of efficacy data is a comprehensive NMA,

and utility values were reported by patients in AMAGINE-1 with baseline PASI ≥ 12 and DLQI > 10, consistent with the NICE definition of severe disease.

B.3.1 Published cost-effectiveness studies

Full details of the process and methods used to identify and select the relevant cost-effectiveness evidence, including PRISMA flow diagram, summary of studies, critical appraisal and quality assessments, are described in Appendix G.

An SLR was performed to identify published economic evaluations that have included brodalumab. This SLR identified one economic evaluation, performed by the US Institute for Clinical and Economic Review, which is summarised in Table 39. Results related to the cost-effectiveness of brodalumab are limited, as the unit cost of brodalumab was not known at the time the work was undertaken. It was not possible to access the model, and therefore a *de novo* model was developed for this submission.

A second SLR was performed with the objective of identifying all relevant economic evaluations of biologic therapies, apremilast, and DMF in moderate-to-severe psoriasis. A total of seven UK-based studies were identified (Table 40), as well as 15 evaluations not based in the UK. Additionally, eight NICE TAs were included in the review (Table 40).

Table 39 Summary of published cost-effectiveness studies of brodalumab

Reference	Country and costing perspective	Study population	Model characteristics/ Type of evaluation	Intervention & Comparators	Time horizon	Outcomes	Sensitivity analysis	Total costs	Total QALYs	Base-case ICERs (Δ£/ΔQALY)[1]
The ICER report (147)	USA, health system perspective	Moderate-to-severe psoriasis	Markov model	Non-targeted therapy ADA APR BRO [a] ETN INF IXE SEC UST	10 years	Total costs, QALYs, and LYs for each therapy. ICER of each targeted therapy vs. non-targeted therapy and ICER of IL-17A targeted drugs vs. ETN	One-way sensitivity analyses and four scenario analyses	Non-targeted: $88,086 ADA: $208,881 Apremilast: $161,741 Brodalumab: $240,398 ETN: $198,519 INF: $203,532 Ixekizumab: $254,287 SEC: $221,704 UST: $269,843	Non-targeted: 5.531 Adalimumab: 6.649 Apremilast: 6.353 Brodalumab: 7.151 Etanercept: 6.469 Infliximab: 6.776 Ixekizumab: 7.187 Secukinumab: 7.018 Ustekinumab: 6.930	*Relative to non-targeted therapy* ADA: $108,040 Apremilast: $89,610 Brodalumab: $94,030 ETN: $117,769 INF: $92,715 Ixekizumab: $100,389 SEC: $89,843 UST: $129,904 *Relative to ETN* Brodalumab: $61,396 Ixekizumab: $77,686 SEC: $42,190

[a] Results for brodalumab are tentative, as pricing was not available at the time of the analysis
ADA, adalimumab; APR, apremilast; BRO, brodalumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; INF, infliximab; IXE, ixekizumab; LYs, life years; QALY, quality-adjusted life-year; SEC, secukinumab; UST, ustekinumab

Table 40 Summary of relevant published cost-effectiveness studies

Reference	Country and costing perspective	Study population	Model characteristics/ Type of evaluation & time horizon	Intervention & Comparators	Outcomes	Sensitivity analysis	Results		
							Total costs	Total QALYs	Base-case ICERs (Δ£/ΔQALY)
Published cost–utility studies of psoriasis treatments in UK									
Woolacott *et al.*, 2006 (148)	UK NHS & PSS	Moderate-to-severe psoriasis	Markov mode, 10 years	BSC EFA (not available in UK) ETN 25 mg BIW cont ETN 25 mg BIW int ETN 50 mg BIW int	Incremental Costs, Incremental QALYs, ICERs	PSA	Relative to BSC ETN 25 mg int: £7,743 EFA: £9,382 ETN 25mg cont: £9,665 ETN 50 mg int: £14,860	Relative to BSC ETN 25 mg int: 0.116 EFA: 0.112 ETN 25 mg cont: 0.116 ETN 50 mg int: 0.123	Base case vs BSC: ETN 25mg cont: £83,258 Scenario 1 (pts with poor DLQI) vs BSC: ETN 25mg cont: £43,479 Scenario 3 (pts with poor DLQI and high risk of hospitalisation) vs BSC: ETN 25mg cont: £23,905

Reference	Country and costing perspective	Study population	Model characteristics/ Type of evaluation & time horizon	Intervention & Comparators	Outcomes	Sensitivity analysis	Results		
							Total costs	Total QALYs	Base-case ICERs (Δ£/ΔQALY)
Lloyd et al, 2009 (149)	UK NHS	Moderate-to-severe psoriasis	Markov model, 10 years	No systemic therapy ETN 25 mg BIW int. ETN 50 mg BIW int.	Total costs, total QALYs, ICERs	Subgroup analyses, scenario analyses, and stochastic analysis using bootstrap resampling to generate 95% CIs	No systemic therapy: £41,985 ETN 25: £44,855 ETN 50: £47,587	No systemic therapy: 0.70 ETN 25: 1.37 ETN 50: 1.61	ETN 50 mg vs. No systemic therapy: £6,217 ETN 25 mg vs. No systemic therapy: £4,297 ETN 50 mg vs. ETN 25 mg: £11,710
Sizto et al, 2009 (150)	UK NHS	Moderate-to-severe psoriasis	Comparison of costs and QALYs; no details or indication of a model structure were provided	BSC MTX CIC EFA ETN 25 mg BIW int. ETN 50 mg BIW int. INF ADA Non-systemics	Incremental Costs, Incremental QALYs, ICERs	OWSA, PSA	*Relative to BSC:* MTX: -£3,844 CIC: -£1,987 ETN 25 mg int: £4,114 ETN 50 mg int: £4,699 EFA: £4,942 ADA: £4,993 ETN: £5,058 INF: £7,736	*Relative to BSC:* MTX: 0.129 CIC: 0.079 ETN 25 mg int: 0.110 ETN 50 mg int: 0.123 EFA: 0.124 ADA: 0.164 ETN 0.134 INF: 0.182	*Relative to BSC:* MTX: -£29,759 CIC: -£25,135 ETN 25 mg int.: £37,284 ETN 50 mg int.: £38,358 EFA: £39,948 ADA: £30,538 ETN: £37,676 INF: £42,492 *Relative to BSC* (excluding traditional systemics): ETN 25 mg and 50 mg and EF: extendedly dominated ADA: £30,538 ETN: Dominated INF: £147,906
Johansson *et al.,*2016 (151)	UK NHS and PSS	Moderate-to-severe psoriasis (PASI≥10 and DLQI>10)	Markov model, lifetime horizon	IXE vs SEC, each followed by sequence of UST 90mg, INF, then BSC	Total cost savings Total QALY gains	OWSA, PSA	IXE sequence: £179,505 SEC sequence: £180,448 Total costs savings for IXE - £943	IXE sequence: 1.45 gained SEC sequence: 1.42 gained Total QALY gains for IXE 0.03	IXE sequence dominates SEC sequence
Mughal *et al.,* 2015 (152)	Scottish payer	Moderate-to-severe psoriasis	Markov model, 10 years	APR sequence: APR – ETN - ADA ADA sequence: ADA - ETN	Total costs Total QALYs	Sensitivity analysis was performed	Incremental cost (APR vs ADA sequence): -£3,206	APR: 7.00 ADA: 6.91	APR sequence dominates ADA sequence
Mughal 2016b (153)	UK payer	Moderate-to-severe psoriasis	Markov model, 10 years	APR sequence: APR - ADA - ETN ADA sequence: ADA - ETN	Total costs, total QALYs, and ICER	A series of sensitivity and scenario analyses and PSA	Incremental cost (APR vs ADA sequence): £1,882	APR: 5.78 ADA: 5.69	APR vs ADA sequence: £20,593

Reference		Country and costing perspective	Study population	Model characteristics/ Type of evaluation & time horizon	Intervention & Comparators	Outcomes	Sensitivity analysis	Results		
								Total costs	Total QALYs	Base-case ICERs (Δ£/ΔQALY)
Sawyer *et al.*, 2015 (154)		UK NHS and PSS	Moderate-to-severe psoriasis and previous exposure to biologic therapy	Decision tree (short-term trial period) Markov model with annual cycles (long - term treatment period), 10 years	Biologic therapy (ADA, ETA, INF, UST) BSC (mix of non-biologic systemic therapies, UVB, specialist topical therapies delivered in dermatology day centres and inpatient care)	Total costs, total QALYs and ICER	Multiple sensitivity and scenario analyses and PSA	Biologic: £99,338 (95% CI: 96,391-102,275) BSC: £93,591 (90,074-97,199) Incremental cost: £5,747 (4,644-6,932)	Biologic therapies: 0.804 (95% CI: 0.514–1.313) BSC:0.479 (0.323–0.669) Incremental benefit: 0.325 (0.124–0.793)	Biologic vs BSC: £17,681
Previous NICE technology appraisals										
TA103 (2006/ 7) (155)	ETN	UK NHS and PSS	Moderate-to-severe psoriasis	Markov model, 96 weeks	ETN 25 mg int. ETN 25 mg BIW cont. ETN 50 mg BIW int. No systemic therapy	Total costs, Total QALYs gained, ICER		12-week analysis: No systemic therapy: £72 ETN 25 mg £3,352 ETN 50 mg £4,474 96-week analysis: No systemic therapy: £578 ETN 25 mg: £8,635 ETN 50 mg: £12,175	12-week analysis: No systemic therapy: 0.011 ETN 25 mg 0.029 ETN 50 mg 0.031 96-week analysis: No systemic therapy: 0.084 ETN 25 mg: 0.236 ETN 50 mg: 0.264	12-week analysis: ETN 25 mg vs no systemic therapy: £124,732 ETN 50 mg vs 25 mg: £1,255,840 96-week analysis: ETN 25 mg vs no systemic therapy: £53,056 ETN 50 mg vs 25 mg: £127,464
	EFA	UK NHS and PSS	Moderate-to-severe psoriasis	Decision tree, 10 years	EFA Topical therapy (Cal/BD)	Total costs, Total QALYs gained, ICER		EFA: £5,611 Topical: £123	EFA: 1.39 Topical: 0.36	EFA vs topical: £25,582
	York model	UK NHS & PSS	Moderate-to-severe psoriasis	Markov model, 10 years	EFA (not available in UK); ETN 25 mg BIW int. ETN 25 mg BIW cont. ETN 50 mg BIW int. BSC Secondary analysis: MTX CIC Fumaderm INF	Incremental Costs, Incremental QALYs, ICERs	Scenario analyses and PSA	Relative to BSC ETN 25 mg int.: £7,743 EFA: £9,382 ETN 25mg (cont): £9,665 ETN 50 mg (int.): £14,860	Relative to BSC ETN 25 mg int: 0.116 EFA: 0.112 ETN 25 mg cont: 0.116 ETN 50 mg int: 0.123	Incremental analysis: ETN 25 mg BIW int vs BSC: £66,703 EFA and ETN 25 mg BIW cont: Dominated ETN 50 mg vs 25 mg BIW int: £1,035,121 Base case vs BSC: ETN 25mg int: £66,703 EFA: £84,018 ETN 25 mg cont: £83,258 ETN 50 mg int: £120,855

Reference	Country and costing perspective	Study population	Model characteristics/ Type of evaluation & time horizon	Intervention & Comparators	Outcomes	Sensitivity analysis	Results		
							Total costs	Total QALYs	Base-case ICERs (Δ£/ΔQALY)
Infliximab NICE TA 134 (2007/8) (156)	UK NHS and PSS	Moderate-to-severe psoriasis (4th quartile DLQI at baseline)	Markov model based closely on the York model by Woolacott et al 2006, 10 years	INF ETN 25 mg BIW cont. ETN 25 mg BIW int. ETN 50 mg BIW int. EFA (no longer available in UK) BSC	Incremental Costs, Incremental QALYs, ICERs	OWSA, PSA	Relative to BSC: ETN 25 mg BIW cont: £1,531 INF: £4,562	Relative to BSC: ETN 25 mg BIW cont: 0.089 INF: 0.205	INF vs BSC: £22,240INF vs ETN 25 mg BIW cont: £26,095
Adalimumab NICE TA 146 (2008) (157)	UK NHS and PSS	Moderate-to-severe psoriasis (DLQI>10)	Markov model based closely on the York model by Woolacott et al 2006, 10 years	ADA MTX CIC INF ETN 25 mg BIW cont. ETN 25 mg BIW int. ETN 50 mg BIW int. EFA (no longer available in UK) BSC	Incremental Costs, Incremental QALYs, ICERs		Relative to BSC: MTX: £3,844 CIC: £1,987 ETN 25 mg BIW int: £4,114 ETN 50 mg BIW int: £4,699 EFA: £4,942 ADA: £4,993 ETA 25 mg BIW cont: £5,058 INF: £7,736	Relative to BSC: MTX: 0.129 CIC: 0.079 ETN 25 mg BIW int: 0.11 ETN 50 mg BIW int: 0.123 EFA: 0.124 ADA: 0.164 ETA 25 mg BIW cont: 0.134 INF: 0.182	Base case vs BSC: MTX: £-29,759 CIC: £-25,135 ETN 25 mg BIW int: £37,284 ETN 50 mg BIW int: £38,358 EFA: £39,948 ADA: £30,538 ETN 25 mg BIW cont: £37,676 INF: £42,492
Ustekinumab NICE TA 180 (2009) (70)	UK NHS and PSS	Moderate-to-severe psoriasis (DLQI>10)	Markov model based closely on the York model by Woolacott et al 2006, 10 years	UST 45 mg UST 90 mg ADA INF ETN 25 mg BIW cont. ETN 25 mg BIW int. ETN 50 mg BIW int. EFA (no longer available in UK) BSC	Incremental Costs, Incremental QALYs, ICERs	OWSA, scenario analyses, subgroup analyses and PSA	Relative to BSC: EFA: £5264 ETN 25 mg BIW int: £3,989 ETN 25 mg BIW cont: £4,829 ETN 50 mg BIW cont: £5,333 ADA: $4,660 UST: £4,615 INF: £6,327	Relative to BSC: EFA: 0.1308 ETN 25 mg BIW int: 0.1325 ETN 25 mg BIW cont: 0.1409 ETN 50 mg BIW cont: 0.1483 ADA: 0.1502 UST: 0.156 INF: 0.1616	Base case vs BSC: EFA: ££40,250 ETN 25 mg BIW int: £30,111 ETN 25 mg BIW cont: £34,281 ETN 50 mg BIW cont: £35,964 ADA: £31,022 UST: £29,587 INF: £39,153
Apremilast NICE TA 368 (2015) (158)	UK NHS and PSS	Moderate-to-severe psoriasis (DLQI>10)	Markov model, 10 years	APR → ADA → ETN → BSC ADA → ETN → BSC	Total costs, total QALYs, ICER	OWSA, scenario analyses, subgroup analyses and PSA	APR sequence: £89,374 Comparator sequence: £92,589	APR sequence: 6.83 Comparator sequence: 6.69	APR sequence dominated comparator sequence
Secukinumab NICE TA 350 (2015) (71)	UK NHS and PSS	Moderate-to-severe psoriasis (DLQI>10)	Decision tree and Markov model based closely on the York model by Woolacott et al 2006, 10 years	SEC ETN 25 mg BIW cont. ADA INF UST 45 mg UST 90 mg BSC	Total costs, total QALYs, ICER	OWSA, scenario analyses and PSA	BSC: £73,610 ETN: £75,788 SEC: £76,361 ADA: £76,981 UST 45 mg: £79,544 UST 90 mg: £79,732 INF: 93,539	BSC: 0.97 ETN: 1.13 SEC: 1.36 ADA: 1.22 UST 45 mg: 1.30 UST 90 mg: 1.33 INF: 1.36	Incremental analysis: SEC vs BSC: £2,464 ETN extendedly dominated ADA, UST 45 mg, UST 90 mg, INF dominated

Reference	Country and costing perspective	Study population	Model characteristics/ Type of evaluation & time horizon	Intervention & Comparators	Outcomes	Sensitivity analysis	Results		
							Total costs	Total QALYs	Base-case ICERs (Δ£/ΔQALY)
Ixekizumab NICE TA 442 (2017) (72)	UK NHS and PSS	Moderate-to-severe psoriasis (DLQI>10)	Markov model, lifetime horizon	IXE → UST90→ INF ADA → UST90→ INF ETN → UST90→ INF INF → UST90→ ADA SEC → UST90→ INF UST45 → ADA →INF UST90 → ADA→ INF	Total costs, total QALYs, ICER	OWSA, scenario analyses, subgroup analyses and PSA	Strategy starting with: ETN: £144,635 UST45: £148,218 ADA: £148,350 UST90: £148,719 INF: £150,350 IXE: £150,889 SEC: £177,101	Strategy starting with: ETN: 1.27 UST45: 1.30 ADA: 1.32 UST90: 1.32 INF: 1.33 IXE: 1.45 SEC: 1.42	Fully incremental analysis: UST (45 and 90), ADA, INF: extendedly dominated SEC dominated IXE vs ETN: £33,848 Base case IXE vs comparator: ETN: £33,858 UST45: £18,278 ADA: £19,202 UST90: £16,763 INF: £4,300 SEC: dominated
Dimethyl Fumarate NICE TA 475 (2017) (159)	UK NHS and PSS	Moderate-to-severe psoriasis	Markov model, 10 years	DMF → ADA → UST → BSC ADA → UST → BSC	Total costs, total QALYs, ICER	OWSA, scenario analyses, subgroup analyses and PSA	Not reported (redacted)	Not reported (redacted)	Incremental analysis: ADA → UST → BSC: Dominated

ADA, adalimumab; APR, apremilast; BIW, twice weekly; BRO, brodalumab; BSC, best supportive care; Cal/BD, Calcipotriol/betamethasone dipropionate; CIC, ciclosporin; DLQI, Dermatology Life Quality Index; EFA, efalizumab; ETN, etanercept; ICER, incremental cost-effectiveness ratio; INF, infliximab; IXE, ixekizumab; LYs, life years; MTX, methotrexate; NHS, National Health Service; OWSA, one-way sensitivity analysis; PASI, Psoriasis Area and Severity Index; PSA, probabilistic sensitivity analysis; PSS, Personal Social Services; QALY, quality-adjusted life-year; SEC, secukinumab; UST, ustekinumab

B.3.2 Economic analysis

A *de novo* model was developed to determine the cost-effectiveness of brodalumab compared with the comparators in the NICE scope. The model was constructed based on the information identified in the literature search described Appendix G.

B.3.2.1 Patient population

Brodalumab is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy. In England and Wales, it is anticipated that brodalumab will be used as per the NICE pathway (1) in the 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). This is, therefore, the population considered in the model.

The patients included in the AMAGINE trials were required to have a baseline PASI ≥ 12, but there was no minimum requirement for DLQI score at enrolment. This is consistent with most recent clinical studies for biologics in psoriasis. Clinical outcomes used to inform brodalumab efficacy in the economic model are pooled from the ITT populations in the five brodalumab trials (AMAGINE-1, -2, -3, Nakagawa 2016 and Papp 2012), in which the mean baseline DLQI score was 14.4 (40, 41, 51, 52). Health state utility estimates used in the base case were based on EQ-5D data from AMAGINE-1 patients with DLQI > 10; this approach is consistent with multiple previous NICE technology appraisals (TAs) (70-72, 157, 158).

The model results are expected to be applicable to a patient population similar to those described in the studies included in the NMA; hypothetical patients in the model are aged 45 years, have a mean weight of 85.8 kg, and are 68% male.

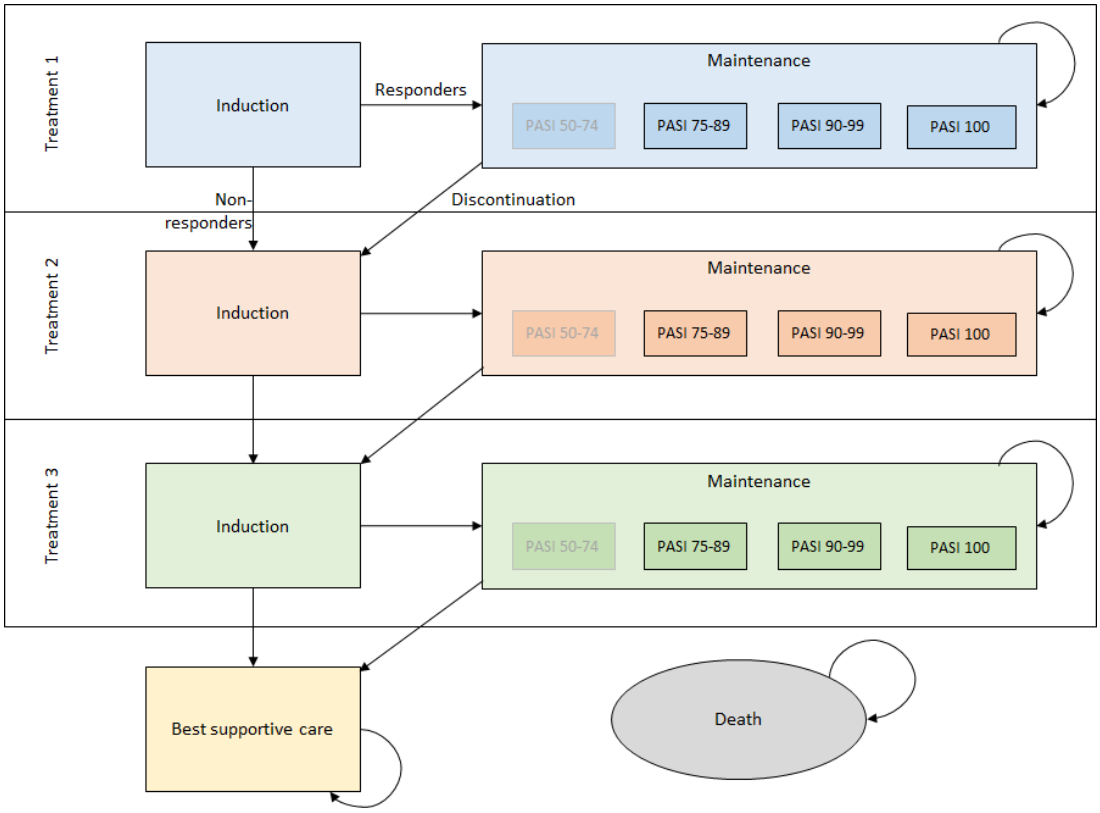
B.3.2.2 Model structure

Model schematic

The model was developed in Microsoft Excel 2013® as a Markov cohort model. The cycle length was 2 weeks and no half-cycle correction was applied. Probabilistic sensitivity analysis (PSA) was incorporated to explore the uncertainty in model variables, using probabilistic distributions.

A schematic diagram illustrating the structure of the model is shown in Figure 29. The model consists of four treatment-related health states defined as induction, maintenance, best supportive care (BSC) and death. In addition, patients can have one of five categories of PASI response: PASI 0-49, PASI 50-74, PASI 75-89, PASI 90-99 or PASI 100.

Figure 29 Schematic model diagram



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

Induction phase

In the induction phase, patients receive active therapies according to approved dosing guidelines (see section.3.2.5). The duration of the induction phase is treatment-dependent, and lasts from 10 to 16 weeks in accordance with response assessment time points reported in NICE TAs guidance (70-72, 155-157).

At the end of the induction period, patients are split among the five PASI response levels, according to the efficacy of the treatment received (see section B.3.3.1). Patients with an adequate response to treatment enter the maintenance phase and continue to receive treatment. Patients without an adequate response switch to the next treatment in the sequence and are assessed again for response following the subsequent induction period.

Maintenance phase

During the maintenance phase, patients continue to receive active therapy, and are assumed to maintain the same level of PASI response until discontinuation. Upon discontinuation, patients are assumed to revert to their baseline PASI score, and switch to the next treatment in the sequence.

Best supportive care

BSC is the final treatment and consists of a bundle of non-biologic supportive therapies. After initiating BSC, all patients continue until the end of the modelled time horizon or death.

Death

Death is an absorbing state to which patients can transition from any model state at any time. Mortality was not conditioned on treatment or level of response and was derived from life tables for England and Wales (see section B.3.3.2).

B.3.2.3 Model characteristics

Type of evaluation: the model takes the form of a cost–utility analysis with a fully incremental analysis. Health outcomes were expressed in terms of quality-adjusted life years (QALYs), and cost outcomes included treatment costs and adverse event costs.

Perspective: the model considers the UK NHS and Personal Social Services perspective, consistent with the NICE reference case.

Time horizon: the time horizon in the base case was set to 40 years, a duration sufficient to capture all relevant costs and benefits of comparator sequences. The impact of a 10-year time horizon on the results of the model were explored in sensitivity analysis.

Discounting: a discount rate of 3.5% was applied to both costs and QALYs, as stipulated by the NICE reference case (160).

Key features

Key features of the analysis, compared with the economic models included in NICE TAs of the comparators (70-72, 155-159), are shown in Table 41.

B.3.2.4 Intervention technology and comparators

The European Commission granted marketing authorisation for brodalumab on 17 July 2017 for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy.

The NICE pathway for psoriasis positions biologics for use after systemic non-biological therapies (1).

Each of the comparator treatments in the base-case analysis are those recommended by NICE for psoriasis patients who have failed to respond to conventional systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or for patients who are intolerant or have a contraindication to these treatments (see section B.1.3.5, Figure 3). NICE recommends infliximab only for patients with very severe psoriasis (defined as a PASI ≥ 20 and DLQI > 18) (1), but for completeness it has been included in the base-case analysis alongside the other therapies recommended by NICE for patients with moderate-to-severe psoriasis.

The comparators were modelled as per their marketing authorisations, NICE endpoints and doses (Table 42). NICE and BAD guidance recommends switching between treatments following a primary or secondary failure, or if a drug cannot be tolerated or becomes contraindicated (1, 2, 29, 56). Sequences of up to three therapy options followed by BSC are considered in the current analysis.

Table 41 Key features of the economic analysis

	Previous appraisals								Current appraisal	
Factor	TA103 ETA	TA134 INF	TA146 ADA	TA180 UST	TA350 SEC	TA419 APR	TA442 IXE	ID776 DMF	Current appraisal values	Justification
Model approach	TA103, TA134, TA146, TA180 and TA350, Decision tree and Markov model TA419, TA442 and ID776, Markov model								Markov model	The Markov structure allows for sequencing of treatments over an extended time horizon
Time horizon	10 years, with the exception of TA442, which used a lifetime horizon								40 years	Patients expected to spend more than 10 years on active treatment, and 40 years is sufficiently long to capture all incremental costs and benefits associated with alternative 3-drug sequences which are assumed to have no impact on mortality
Cycle length	Variable: TA103 and TA350, 12 months; TA180, 3 months; TA419, 4 weeks; TA442, 1 month; ID776, 2 weeks								2 weeks	Captures variable induction periods when patients are assessed for response and either continue or switch treatments
Treatment waning effect?	Treatment effect was assumed to be maintained with ongoing treatment. Treatment efficacy was assumed to be the same regardless of exposure to prior therapies.								Treatment effect was assumed to be maintained with ongoing treatment. Treatment efficacy was assumed to be the same regardless of exposure to prior therapies.	Evidence on the maintenance of PASI response in the long-term is lacking. In its absence, it was assumed that patients maintain PASI response achieved at induction until they discontinue. Registry data suggests that the biggest driver of long-term discontinuation is loss of response, so it is assumed that those who stop responding would be included among annual drop-outs and that those who continue do so while their response is maintained The placement of a drug within a sequence is not assumed to have any impact on its efficacy. Results of subgroup analyses from the AMAGINE trials showed that the efficacy of brodalumab was similar in patients with and without exposure to prior therapies, a finding that is similar to evidence presented in previous TAs of psoriasis treatments

	Previous appraisals								Current appraisal	
Factor	TA103 ETA	TA134 INF	TA146 ADA	TA180 UST	TA350 SEC	TA419 APR	TA442 IXE	ID776 DMF	Current appraisal values	Justification
Source of utilities	TA103, analysis of patient-level data from 3 ETA RCTs and a regression analysis of EQ-5D and DLQI from the HODaR database TA134, TA419, ID776, values used in TA103 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								A least squares regression model of AMAGINE-1 assessed relationship between change in EQ-5D, PASI response level and baseline DLQI	EQ-5D data collected alongside efficacy measurements in the AMAGINE-1 trial were considered the most robust source of utility data for the CEA of brodalumab. Utility values were calculated using UK preference weights for the EQ-5D-3L. Alternative values were used in sensitivity analysis
Source of resource use	TA103, TA134, TA146 and TA180, Woolacott 2006; TA350 and TA419, CG153; TA442, CG153 and Fonia 2010; ID776, not specified								CG153, BAD guidelines, Fonia 2010	Consistent with most recent TAs and current guidance
Source of unit costs	All appraisals: NHS reference costs and PSSRU. In addition: TA103, TA134, TA146, TA180, TA350 and TA419, BNF; TA442 and ID776, MIMS								NHS reference costs, PSSRU, MIMS	Consistent with NICE reference case
Adverse events	TA103, TA134, TA146, TA180, TA419 and AD776, not included TA350, impact of AEs (NMSC, malignancies other than NMSC, severe infections) on costs included TA442, Impact of AEs (NMSC, malignancies other than NMSC, severe infections) on costs included in scenario analysis only								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	Modelled therapies have immunomodulatory or immunosuppressive effects that put patients at risk for serious infections. Evidence on their incidence was available for most drugs and their impact on costs and QALYs could be reasonably quantified
Mortality	TA103, TA134, TA146, TA180 and TA419, not included TA350, TA442 and ID776, included, not disease- or treatment-dependent								Included, not treatment-dependent	All-cause mortality is applied in the model, and is adjusted to account for the increased risk of death among patients with moderate-to-severe psoriasis face relative to matched controls. No evidence is available to indicate that treatment has any effect on mortality

ADA, adalimumab; AE, adverse event; APR, apremilast; BAD, British Association of Dermatologists; BNF, British National Formulary; CG, Clinical Guideline; CEA, cost-effectiveness analysis; DLQI, Dermatology Life Quality Index; DMF, dimethyl fumarate; EQ-5D, EuroQol 5 dimensions; ETN, etanercept; HODaR, Health Outcomes Data Repository; INF, infliximab; IXE, ixekizumab; MACE, major adverse cardiovascular events; MIMS, Monthly Index of Medical Specialties; NMSC, non-malignant skin cancer; PSSRU, Personal Social Services Research Unit; SEC, secukinumab; TA, technology appraisal; UST, ustekinumab

Table 42 Dosing regimens, stopping rules and model doses

Treatment	Dosing instruction	Stopping rule – NICE	Stopping rule – SmPC	Induction period duration	Number of induction period doses	Total doses in year 1	Annual number of maintenance doses
Brodalumab	Injection of 210 mg on day 1 and weeks 1 and 2 and then every other week thereafter		Consideration should be given to discontinuing treatment in patients who have shown no response after 12 to 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks	12 weeks	7	27	26
Adalimumab	Injection, initially 80 mg, then 40 mg on alternate weeks starting 1 week after initial dose	Should be discontinued in people whose psoriasis has not responded adequately at 16 weeks	Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this period	16 weeks	10	28	26
Apremilast	30 mg twice daily after an initial titration schedule	Should be discontinued in people whose psoriasis has not responded adequately at 16 weeks	If a patient shows no evidence of therapeutic benefit after 24 weeks, treatment should be reconsidered	16 weeks	109.5	361.75	364.25
Dimethyl fumarate	The maximum dosage is 240 mg three times daily given orally, after an initial titration schedule	Should be discontinued in people whose psoriasis has not responded adequately at 16 weeks		16 weeks	75.25	327.5	364.25
Etanercept [a]	Injection, 25 mg twice weekly or 50 mg once weekly, for up to 24 weeks	Should be discontinued in people whose psoriasis has not responded adequately at 12 weeks	Treatment should be discontinued in patients who show no response after 12 weeks	12 weeks	12	52	52

Treatment	Dosing instruction	Stopping rule – NICE	Stopping rule – SmPC	Induction period duration	Number of induction period doses	Total doses in year 1	Annual number of maintenance doses
Infliximab	By IV infusion, 5 mg/kg, repeated 2 weeks and 6 weeks after initial infusion, then every 8 weeks	Should be discontinued in people whose psoriasis has not responded adequately at 10 weeks	If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given	10 weeks	3	8	6.5
Ixekizumab	Injection, initially 160 mg, then 80 mg every two weeks for 12 weeks. Maintenance: 80 mg every 4 weeks	Should be discontinued in people whose psoriasis has not responded adequately at 12 weeks	Consideration should be given to discontinuing treatment in patients who have shown no response after 16 to 20 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 20 weeks	12 weeks	7	17	13
Secukinumab	Injection of 300 mg at weeks 0, 1, 2 and 3 followed by monthly dosing from week 4. Each 300 mg injection is administered as two injections of 150 mg	Should be discontinued in people whose psoriasis has not responded adequately at 12 weeks	Consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment	12 weeks	6	16	12
Ustekinumab	Injection, body weight < 100 kg, initially 45 mg, then 45 mg 4 weeks after initial dose, then 45 mg every 12 weeks. Bodyweight >100 kg, initially 90 mg, then 90 mg 4 weeks after initial dose, then 45 mg every 12 weeks	Should be discontinued in people whose psoriasis has not responded adequately at 16 weeks	Consideration should be given to discontinuing treatment in patients who have shown no response up to 26 weeks of treatment	16 weeks	2	5	4.33

[a] Etanercept is available in two doses: 50 mg per week (administered as either 25 mg twice weekly or 50 mg once weekly) and 100 mg per week (administered as 50 mg twice weekly). Only the lower dose is recommended by NICE; therefore, only this dose has been included in the base-case analysis. SmPC, summary of product characteristics.

B.3.2.5 Treatment sequences

The treatment sequences included in the model (Table 43) comprise three lines of active therapy, followed by BSC. The first position of each treatment sequence is occupied by one of the comparators of brodalumab in line with the TA scope. The 2017 BAD guidelines, corroborated with clinical expert opinion from an English advisory board made up of clinical and health economic experts, were used to construct the sequences modelled in the base-case analysis.

Where possible, second- and third-line therapies were selected that had a different mechanism of action to the preceding line (e.g. patients discontinuing therapy with an anti-TNF agent are not then treated with a subsequent anti-TNF therapy); this approach is consistent with the recent ixekizumab TA (72).

The 2017 BAD guidelines include recommendations to offer adalimumab or ustekinumab and to consider secukinumab as first-line biologic agents (56). Of these three therapies, the advisory board considered adalimumab to be the likeliest first-line biologic candidate given its familiarity, lower unit cost and usefulness among patients with co-morbid psoriatic arthritis. UK market share data supports this positioning (72).

The advisory board indicated that ustekinumab was likely to be used second-line, on the basis of familiarity and cost. This positioning is consistent with the 2017 BAD guidance (56). In the model, it is therefore used as a common second-line therapy across sequences.

Secukinumab was selected to be a common third-line treatment based on the 2017 BAD recommendation (56). This sequence is consistent with Clinical Commissioning Group (CCG) guidance on treatment sequencing in psoriasis (161). Use of infliximab as an alternative third-line therapy was tested in sensitivity analysis.

Where ustekinumab is positioned first, adalimumab is selected as the second-line option. Similarly, for the sequence starting with secukinumab, adalimumab is used as the third-line treatment.

Table 43 Comparator sequences – base case

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

BSC, best supportive care; DMF, dimethyl fumarate

Given the large number of licensed therapies for moderate-to-severe psoriasis, other treatment sequences are possible, and may be used in clinical practice. These might include the use of biological therapies in a different order, or the use of more than three lines of

therapy (particularly in the case of first-line therapy with the non-biological agents apremilast and DMF). However, the priority for the cost-effectiveness analysis was to construct treatment sequences that would aid the comparison of brodalumab with the comparators included in the final scope. Therefore, to ensure the model results were useful for decision-making, maintaining a common second- and third-line treatment algorithm across sequences where possible was considered to be more important than including all possible treatment combinations.

Overall, this approach to treatment sequencing is consistent with the economic model included in the recent TAs for ixekizumab (72).

B.2.3.6 Treatment continuation

In the model, continuation of treatment is dependent on response at the end of the induction period. The induction period is treatment-dependent and consistent with the time point for response assessment in NICE guidance for each currently recommended therapy (Table 42). The SmPC for brodalumab indicates treatment continuation should be assessed over 12 to 16 weeks; the model assumes that assessment of response occurs at week 12, corresponding to the induction dosing period in the AMAGINE trial programme.

Treatment response is defined in CG153 and BAD guidelines for psoriasis as achieving at least (2, 29, 56):

- PASI 75; or
- PASI 50 and a 5-point decrease in DLQI.

PASI 75 is the most frequently used primary efficacy measure in clinical trials and has been employed in all previous NICE TAs as the only base-case response criterion for treatment continuation. In the current analysis, patients must achieve a minimum of PASI 75 to move on to maintenance treatment. The alternative continuation rule, PASI 50 and a 5-point decrease in DLQI, is not implemented in the model due to a lack of data for all comparators on this combined measure; therefore, it is not possible to include this as a response criterion. Instead, using PASI 50 alone as a treatment continuation threshold is tested in a scenario analysis.

Treatment continuation in the maintenance phase is not dependent on response. In line with previous economic evaluations and all NICE TAs, the model assumes that patients discontinue treatment at a constant annual rate (see section B.3.3.1). This represents all-cause discontinuation due to loss of response and adverse events.

B.3.3 Clinical parameters and variables

B.3.3.1 Clinical data

PASI responses

In the base-case analysis, treatment is assumed to continue for the duration of the induction period (10–16 weeks). During the induction period, patients were distributed across five PASI response levels based on the results of the base-case NMA. The overlapping, nested PASI categories derived from the NMA were transformed into mutually exclusive categories at the reported cut-offs (0–49, 50–74, 75–89, 90–99, 100). A multinomial likelihood NMA setup with probit link function was used to simultaneously calculate the probability of PASI 50, 75, 90 and 100 responses and the relative risk between each comparison in the network (see section B.2.9). The proportion of patients in each PASI category is shown in Table 44.

Table 44 Proportion of patients in each PASI response category at the end of the induction period

Treatment	Induction period duration (weeks)	Treatment effect estimate (SE)[a,b]	PASI 0–49	PASI 50–74	PASI 75–89	PASI 90–99	PASI 100
Brodalumab	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	16	–1.99 (0.07)	0.17	0.17	0.26	0.25	0.15
Apremilast	16	–0.97 (0.08)	0.53	0.20	0.17	0.08	0.02
Dimethyl fumarate	16	–0.71 (0.16)	0.63	0.17	0.13	0.05	0.01
Etanercept 50 mg / week	12	–1.3 (0.07)	0.40	0.20	0.21	0.14	0.05
Infliximab	10	–2.39 (0.09)	0.09	0.12	0.23	0.30	0.26
Ixekizumab	12	–2.88 (0.07)	0.03	0.06	0.17	0.30	0.44
Secukinumab	12	–2.56 (0.07)	0.07	0.10	0.21	0.31	0.32
Ustekinumab [c]	16	–2.13 (0.07)	0.14	0.15	0.25	0.27	0.18
BSC	NA	0 (NA)	0.85	0.09	0.04	0.01	0.00

BSC, Best Supportive Care; NA, not applicable; PASI, Psoriasis Area and Severity Index.
[a] probit scale
[b] Median PASI cut-off points on probit scale (SE): 50, 1.05 (0.05); 75, 0.53 (0.01); 90, 1.19 (0.01); 100, 1.99 (0.02)
[c]Based on weight-based dose (45 mg if patient weighs <100kg; 90 mg if >100 kg).

At the end of the trial period, patients continued treatment if they had achieved a PASI response of 75% or higher. These responders were assumed to maintain their response for as long as they were on maintenance therapy. Patients with a response lower than PASI 75 were deemed treatment non-responders and immediately switched to the next treatment in the sequence. A response threshold of PASI 50 is explored in a scenario analysis (see section B.3.8.3).

Once patients entered BSC, they were distributed across the five health states based on the placebo responses from the NMA (Table 44) and remained there until the end of the modelled time horizon, or death.

Prior biologic treatment

A Danish registry study found that prior failure of a biologic therapy was a significant predictor of biologic discontinuation (34). However, other registry and observational studies have found no statistically significant association between drug survival and previous biologic exposure (162-164). The feasibility of performing an NMA among patients with prior biologic exposure or failure was assessed, but evidence was insufficient to perform a robust analysis. Subgroup analyses using pooled patient population data from the AMAGINE trials found that the efficacy of brodalumab was consistent across different prior treatment subgroups during the induction period (see section B.2.7.2), a finding similar to that presented in the secukinumab and ixekizumab TA submissions (71, 72).

In the absence of an NMA in the subgroup of patients with prior biologic exposure or definitive evidence that the efficacy of brodalumab is influenced by prior treatment, in the base case analysis prior biologic treatment was assumed not to be an effect modifier. This assumption applied to all therapies included in the analysis and was varied in sensitivity analysis.

Discontinuation

In the base-case analysis, treatment discontinuation was assumed to be the same for all therapies. According to data from the BADBIR registry (33), 23% of patients being treated with a first biologic discontinue by the end of year 1. Another 14% discontinue during year 2, followed by a further 10% in year 3. The higher rate of discontinuation during the first year may include patients who stop treatment following a primary non-response. To avoid double counting discontinuations due to early non-response, the annual discontinuation rate for the model was calculated using data only from years 2 and 3. The model assumed that time to discontinuation followed an exponential model with a constant annual probability of 18.7% (Table 45).

Assuming the same discontinuation rate for all therapies may be a conservative approach. Because the BADBIR registry found a lower rate of discontinuation with ustekinumab than with anti-TNF therapies, a scenario analysis (see section B.3.8.3) was performed in which IL-inhibitors (brodalumab, ixekizumab, secukinumab and ustekinumab) were assumed to have a lower annual probability of discontinuation than subcutaneous anti-TNF therapies (adalimumab, etanercept and infliximab). The discontinuation rate for adalimumab, which was the most commonly used anti-TNF in the BADBIR population, was assumed to represent the rate for all three anti-TNFs (Table 45). No data on discontinuation rates for apremilast and dimethyl fumarate were available and it was assumed that they were similar to those for anti-TNFs.

The approach to estimating discontinuation and the resulting probabilities were presented to an advisory board of clinicians and health economic experts who agreed that both were appropriate, as was the assumption not to differentiate between therapies in the base case.

Table 45 Treatment discontinuation for any reason

Drug class	Annual probability	Source	Notes
Base case: equal discontinuation			
All drugs	18.7%	Warren *et al.* 2015 (33)	Calculated from probabilities still on treatment with any drug in years 2 and 3 [a]
Scenario analysis 4: drug class dependent discontinuation			
Anti-TNF	14.6%	Warren *et al.* 2015 (33)	Calculated from probabilities still on treatment with adalimumab in years 2 and 3 [b]
IL-inhibitor	7.3%	Warren *et al.* 2015 (33)	Calculated by applying a hazard ratio for ustekinumab vs adalimumab: 0.48 (95% CI: 0.38–0.62)

[a] 77% of patients treated any biologic were still on therapy after 1 year, 63% after 2 years and 53% after 3 years. Annual discontinuation after year 1 was calculated by fitting an exponential model to these data points.
[b] 79% of patients treated with adalimumab were still on therapy after 1 year, 7% after 2 years and 59% after 3 years. Annual discontinuation after year 1 was calculated as by fitting an exponential model to these data points.
TNF, tumour necrosis factor; IL, interleukin; CI, confidence interval.

Adverse events

Adverse events were included in the analysis if their management was deemed to have a large impact on costs. It was assumed that this would include any serious adverse events, defined as those events which are life threatening, or which lead to hospitalisation or other medical emergencies.

The immunomodulatory or immunosuppressive effects associated with these treatments may predispose patients to potential adverse events (165-168). The reporting of serious adverse events varied widely across the clinical evidence base. However, serious infections were commonly reported, and were the most common serious adverse event reported for both biologic and conventional systemic therapies.

The risk of serious infections is reported to be different across therapies (169-172). However, clinical trials are not powered to detect such rare events and often include placebo-control observations for only a short duration (the induction phase, 12–16 weeks).

To inform the model of the risk of serious infections with each biologic treatment and BSC we used evidence from a large international, long-term, prospective, disease-based registry, enrolling patients with psoriasis who are receiving, or are candidates for, treatment with systemic therapies: the Psoriasis Longitudinal Assessment and Registry (PSOLAR) study. In Kalb *et al*. 2015 (173) data were reported for 11,466 patients, reflecting 22,311 patient-years (overall population consisted): 9,154 had received a biological agent, 490 had received methotrexate (and possibly other non-biologic systemic therapies), and 1,610 had received therapy other than methotrexate and biologics during the registry.

Kalb *et al.* 2015 (173) present the cumulative incidence of serious infections per 100 patient-years in the overall population for ustekinumab, infliximab, etanercept, and adalimumab (see Table 46). Non-biologic therapies included (but were not limited to) methotrexate, systemic retinoids, psoralen plus UV-A, and UV-B, which may also impact infection risk in different ways and to different degrees. Two non-biological therapy groups were reported:

- Non-methotrexate/non-biologic, which includes patients who never received methotrexate or biologic

- Methotrexate/non-biologic which includes patients who never received biologic but have received methotrexate

The rates of serious infection associated with the non-MTX/non-biologic population were assumed to be representative of BSC in the economic model.

Data for other drugs, including apremilast, dimethyl fumarate, ixekizumab, secukinumab and brodalumab, were not available in the Kalb *et al.* study (173). The rates of serious infection associated with the methotrexate/non-biologic population were assumed to represent apremilast and dimethyl fumarate, both oral systemic medications like methotrexate. Week 52 safety results from the CLEAR study (secukinumab vs ustekinumab) (82) and week 24 safety results from the IXORA-S study (ixekizumab vs ustekinumab) (174) indicated there to be no statistically significant differences between the drugs in the incidence of serious adverse events overall or of infections (serious or non-serious). It was therefore assumed that the ustekinumab risk from the PSOLAR study was representative of the risk for secukinumab and ixekizumab.

To estimate the risk of serious infections with brodalumab, data from week 52 of AMAGINE-2 and AMAGINE-3 were used (40). Rates of serious infections for brodalumab (4/380 patient-years in AMAGINE-2; 7/384 patient-years in AMAGINE-3) versus ustekinumab (2/246 patient-years in AMAGINE-2; 3/249 patient-years in AMAGINE-3) were meta-analysed to give a rate ratio of 1.43 (95% CI: 0.5, 4.08). This rate ratio was applied to the ustekinumab risk from the PSOLAR study to give an estimated rate of serious infections with brodalumab 1.19 per 100 patient-years (Table 46). As there was no statistically significant difference between the AMAGINE brodalumab and ustekinumab arms, this is likely to be a conservative approach.

Table 46 Rate of serious infections used in the economic model

Drug	Serious infection rate (per 100 patient-years)	Source
BSC	1.05 (0.75–1.43)	Kalb 2015 (non-methotrexate/non-biologic population value) (173)
Adalimumab	1.97 (1.61–2.39)	Kalb 2015 (173)
Etanercept	1.47 (1.10–1.91)	Kalb 2015 (173)
Infliximab	2.49 (1.88–3.23)	Kalb 2015 (173)
Ustekinumab	0.83 (0.61–1.09)	Kalb 2015 (173)
Brodalumab	1.19	Calculated by applying brodalumab vs ustekinumab rate ratio (1.43, 95% CI 0.5 to 4.08) meta-analysed from rate of serious infections at 52 weeks in AMAGINE-2 and AMAGINE-3 (40) to ustekinumab rate.
Secukinumab	0.83 (0.61–1.09)	Assumed same as ustekinumab based on similarity across serious AEs, infections and upper respiratory tract infections at 52 weeks in CLEAR (82, 175)
Ixekizumab	0.83 (0.61–1.09)	Assumed same as ustekinumab based on similarity across nonfatal serious AE and infections at 24 weeks in IXORA-S (Reich 2017) (174)
Apremilast	1.28 (0.73–2.09)	Kalb 2015 (non-methotrexate/non-biologic population value) (173)
DMF	1.28 (0.73–2.09)	Kalb 2015 (non-methotrexate/non-biologic population value) (173)

BSC, best supportive care; DMF, dimethyl fumarate.

The inclusion of other adverse events, including non-melanoma skin cancer (NMSC), malignancies other than NMSC, and major adverse cardiovascular events (MACE), was considered. A targeted search for meta-analyses of these events showed there to be insufficient evidence to differentiate between treatments (176-178) – therefore, they were included only in a scenario analysis only. Rates of these events are described in section B.3.8.3.

B.3.3.2 Transition probabilities

In the absence of data to model time-dependent transition probabilities after induction, the model used fixed transition probabilities for PASI response rates from the induction period into maintenance and a constant discontinuation rate from maintenance therapy back to induction of the next treatment in the sequence. Only death was dependent on time and population characteristics such as age and gender.

Induction phase to maintenance phase

After starting induction treatment, patients were assumed to move through a series of temporary tunnel states unless they died. At the end of the induction phase, patients were assessed for response and those with a greater than PASI 75 response transitioned to the maintenance phase. Those not achieving a PASI 75 response transitioned to the induction period for the next treatment in the sequence. The duration of the induction period was variable according to NICE TAs guidance (70-72, 155-157).

Maintenance treatment to induction of next treatment in sequence

Patients entering the maintenance phase following PASI 75 response to induction treatment were assumed to continue treatment until they discontinued for any reason. A constant annual dropout rate of 18.7% was converted into a 2-weekly dropout rate of 0.79% as follows, and it was applied in each model cycle to patients receiving any therapy.

$$p_{cycle} = 1 - e^{\left(\frac{ln(1-p_{annual})}{26}\right)}$$

Mortality

Life expectancy estimates were derived from an analysis of GPRD data on 3,951 patients with severe psoriasis and 15,075 matched control individuals (15). The study found that for all ages over 18 years, the mortality rate for the control group was 12 cases per 1,000 patient-years. The excess deaths in the severe psoriasis group were 6 cases per 1,000 patient-years. After adjustments for other major risk factors of death, the hazard ratio (HR) was estimated to be 1.42 (95% CI, 1.25-1.62). This HR was applied to age-dependent all-cause mortality rates obtained from UK life tables (179), and applied as a background risk of death to all patients. To reflect the patient population in the model, the gender-specific mortality rate was combined into a blended rate, using the proportion of males across the trials included in the NMA (68%).

Psoriasis treatment was assumed not to have any effect on overall mortality.

These assumptions were validated by an advisory board made up of clinical and health economic experts.

B.3.4 Measurement and valuation of health effects

Health effects in the current analysis were expressed in QALYs, in accordance with the NICE reference case.

B.3.4.1 Health-related quality of life data from clinical trials

Utility values for moderate-to-severe psoriasis and for the five categories of PASI response following treatment were calculated from EQ-5D results reported by patients in the AMAGINE-1 trial of brodalumab 210 mg Q2W versus placebo (utilities were calculated using UK preference weights for the EQ-5D-3L; see section B.2.6.3.5).

The change in EQ-5D score from baseline to week 12 was calculated for each patient, pooled across treatment arms and stratified by the level of PASI response.

The extent to which PASI response category affected change from baseline EQ-5D utility in AMAGINE-1 was estimated using a least squares regression model. Change in EQ-5D from baseline to 12 weeks was modelled as a function of PASI response at week 12 and baseline DLQI, as follows:

EQ-5D regression model, adjusted for baseline DLQI

$$\Delta\text{EQ-5D}=\alpha+\beta_1\text{PASIresponse}+\beta_2\text{DLQIbaseline}$$

Two analyses were performed. In the first, all patients for whom EQ-5D data were available were included in the analysis of variance (ANOVA) model approach. A complete case analysis approach resulted in a regression model based on data from 617 patients. In a subgroup analysis, 401 patients with a baseline DLQI > 10 for whom EQ-5D data were available were included in the regression. The criterion for the subgroup aligns the estimates of HRQoL with the definition of moderate-to-severe psoriasis as described in NICE Clinical Guideline 153 (2).

Parameter estimates for the intercept and PASI response categories in the “all patients” and DLQI > 10 patient group are presented in Table 47. No response was the reference category, therefore the coefficients for the intercept and baseline DLQI, α and β_2, correspond to the improvement from baseline EQ-5D associated with a < 50% improvement on PASI. The coefficient β_1 represents the gain in EQ-5D for achieving a higher response level. As expected, PASI 50–74 response was associated with the smallest gain in EQ-5D and PASI 100 with the largest.

Utility gains were dependent on the level of PASI response achieved as a result of treatment, and no other health effects were explicitly modelled. In the base-case analysis, utility values for patients with a baseline DLQI score of > 10 were used (section B.3.4.4, Table 49) – this is consistent with the definition of moderate-to-severe psoriasis described in

NICE Clinical Guideline 153 (2) which is used to identify patients who should be offered biological therapy. Use of utility values based on data for all patients in AMAGINE-1 was explored in a scenario analysis (see section B.3.8.3).

Table 47 Parameter coefficients from ANOVA models, complete cases

ANOVA model	Coefficient	Standard error
All patients (scenario analysis)		
Intercept	−0.1910	0.02659
PASI 50–74	0.1305	0.04095
PASI 75–89	0.2397	0.03578
PASI 90–99	0.2754	0.03119
PASI 100	0.2853	0.02786
Baseline DLQI	0.01386	0.001496
DLQI>10 (base case analysis)		
Intercept	−0.3254	0.05513
PASI 50–74	0.1740	0.05482
PASI 75–89	0.2788	0.04910
PASI 90–99	0.3394	0.04201
PASI 100	0.3522	0.04012
Baseline DLQI	0.01885	0.002852

ANOVA, analysis of variance; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index.

It was assumed that patients accrued health utility gains relative to baseline during the induction period and that these gains continued to accrue among responders who enter the maintenance period.

B.3.4.3 Mapping

No mapping was needed to assess health state utility values as EQ-5D data were collected in the AMAGINE-1 clinical trial.

B.3.4.3 Health-related quality of life studies

A series of SLRs were conducted to identify relevant health utility elicitation/validation studies and mapping algorithms. Details of the search strategy, inclusion criteria and individual study results are described in Appendix H.

An SLR of HRQoL evidence was performed on 2nd October 2014, to support the NICE assessment of secukinumab (Cosentyx®, Novartis) for patients with moderate-to-severe psoriasis (TA350) (71). This SLR identified eight relevant studies. The Evidence Review Group (ERG) concluded that, “the report was written in a clear manner and included relevant studies to address the objectives of this assessment.” Therefore, it was concluded that all relevant HRQoL evidence was identified up to the date of the HRQoL search.

To identify more recent evidence, searches were performed on the 31st January 2017 and updated on 15th August 2017.

A summary of the identified EQ-5D utility values, including those used in previous STA submissions, is presented in Table 48. Values used in the current submission generally lie within the range of estimates identified from the SLR and in previous NICE TAs.

Table 48 Summary of EQ-5D utility values by health state, as identified in SLR, previous technology appraisals and the current submission

		Baseline	PASI < 50	PASI 50–74	PASI 75–89	PASI 90–99	PASI 100	Comments
Utility values by health state								
Knight *et al.* 2012 [d] (180)		NR	0.66	0.861	0.892	0.892	NR	PASI 14–74 response was given a utility value of 0.761. Utility scores that were derived from mapping from DLQI scores for each health state
Sherif *et al.* 2017 (181)	Patients in CLEAR trial	NR	0.801 (SE 0.0090)	0.850 (SE 0.0068)	0.880 (SE 0.0062)	PASI 90-100 0.908 (SE 0.0053)	0.910 (SE 0.0060)	This publication is a poster and therefore does not provide all the study details Data in the PASI 90 to < 100 column in this study include PASI 100. This explains the small difference in these scores compared to the PASI 100 scores
Utility gains from baseline to end of induction by health state								
Woolacott et al, 2006 (148) Etanercept and Efalizumab (TA 103) [a] (155)	All patients	NR	0.05 (SE 0.01)	0.17 (SE 0.04)	0.19 (SE 0.04)	0.21 (SE 0.05)	NR	Data from all patients used. Mapping was used to calculate the mean gain in utility for the various PASI response categories
	4th quartile DLQI	NR	0.12 (SE 0.03)	0.29 (SE 0.06)	0.38 (SE 0.08)	0.41 (SE 0.09)	NR	Mean gains in utility for the different PASI response categories for patients in the 4th quartile DLQI: (a proxy for moderate-to-severe psoriasis)
Shikiar et al, 2006 [b] (69)	Patients with moderate-to-severe plaque psoriasis and BSA of ≥ 5%	NR	–0.01 (SD 0.26, PASI < 25)	0.2 (SD 0.21)	0.25 (SD 0.30)	0.25 (SD 0.30)	NR	Change in Index EQ-5D score
			0.1 (SD 0.24, PASI 25-49)					
Anis et al, 2011 [e] (182)	Moderate-to-severe psoriasis	NR	0.04 (SE 0.02)	0.12 (SE 0.02)	0.12 (SE 0.02)	0.21 (SE 0.02)	NR	Change in Index EQ-5D score
Pickard *et al*., 2017 (183)	EQ-5D-3L crosswalk UK DLQI>10	0.660	0.029 (SE 0.010)	0.125 (SE 0.016)	0.166 (SE 0.012)	0.184 (SE 0.010)	0.189 (SE 0.011)	Change in health utility derived from EQ-5D collected in UNCOVER-1, -2 and -3
	EQ-5D-5L England DLQI>10	0.761	0.029 (SE 0.009)	0.094 (SE 0.013)	0.130 (SE 0.011)	0.139 (SE 0.009)	0.141 (SE 0.009)	

		Baseline	PASI < 50	PASI 50–74	PASI 75–89	PASI 90–99	PASI 100	Comments
Infliximab (TA134) [e] (156)	4th quartile DLQI	NR	0.12 (SE 0.03)	0.29 (SE 0.06)	0.38 (SE 0.08)	0.41 (SE 0.09)	NR	Same as Woolacott *et al.* 2006 (148)
Adalimumab (TA146) (157), Sizto *et al.* 2009 [e] (150)	All patients	NR	0.054 (SE 0.017)	0.14 (SE 0.016)	0.14 (SE 0.016)	0.219 (SE 0.021)	NR	EQ-5D collected alongside RCTs, utility gains used within the CEA
	DLQI ≤ 10	NR	0.045 (SE 0.024)	0.102 (SE 0.022)	0.102 (SE 0.022)	0.13 (SE 0.031)	NR	
	DLQI > 10	NR	0.063 (SE 0.025)	0.178 (SE 0.023)	0.178 (SE 0.023)	0.308 (SE 0.027)	NR	
Ustekinumab (TA180) (70), Pan *et al.* 2011 [c,e] (184)	DLQI > 10	NR	0.04	0.17	0.22	0.25	NR	Mapping was used in order to calculate the mean gain in utility for the various PASI response categories
Secukinumab (TA350) (71)	DLQI>10	NR	0.11	0.19	0.23	0.26	NR	EQ-5D collected alongside RCTs, utility gains used within the CEA
Apremilast (TA368) (158)	All patients	0.7	0.05 (SE 0.010)	0.17 (SE 0.041)	0.19 (SE 0.041)	0.21 (SE 0.051)	NR	Change in utility values from Woolacott *et al.,* 2006 (148); baseline utility value from Revicki *et al.,* 2008 (185)
Ixekizumab (TA442) (72)	DLQI>10	NR	0.0123 (SE 0.006)	0.100 (SE 0.010)	0.131 (SE 0.008)	0.144 (SE 0.007)	0.153 (SE 0.007)	EQ-5D-5L collected alongside RCTs, utility gains used within the CEA
Dimethyl fumarate (TA 475) (159)	All patients	0.7	0.05 (SE 0.010)	0.17 (SE 0.041)	0.19 (SE 0.041)	0.21 (SE 0.051)	NR	Change in utility values from Woolacott *et al.,* 2006 (148); baseline utility value from Revicki *et al.,* 2008 (185)
Present submission	DLQI > 10	0.5206	0.0158	0.1898	0.2946	0.3552	0.3680	EQ-5D-5L collected in AMAGINE-1, utility gains used within the CEA
	All patients	0.6105	0.0044	0.1349	0.2441	0.2798	0.2897	

[a] Data from all patients used
[b] Different PASI response levels used. These are PASI <25, PASI 25-49, PASI 50-74 and PASI 75 and above
[c] PHOENIX trial only
[d] Change in EQ-5D is the dependent variable in the regression analysis
[e] Absolute EQ-5D is the dependent variable in the regression analysis
CI, confidence interval; DLQI, Dermatology Quality of Life Index; EQ-5D, European Quality of Life 5-Dimension Health Questionnaire; EQ-5D-5L, European Quality of Life – 5 Dimensions, 5 levels; NR, not reported; PASI, Psoriasis Area and Severity Index; SD, standard deviation; SE, standard error; VAS, visual analogue scale.

Adverse reactions

Serious infection was the only adverse event considered in the base case. The HRQoL impact associated with serious infection has been modelled by applying a utility multiplier from the literature to the utility of patients experiencing the event (186). Diamantopoulos *et al*. 2014 estimated this degradation of utility based on a study by Sisk *et al*. 1997 (187). The multiplier (0.9858) was calculated using a utility for pneumonia (0.21) and adjusting it for the expected duration of the event (7 days) and the baseline age and gender of the Sisk *et al.* cohort (186).

Adverse events such as NMSC, malignancies other than NMSC, and MACE are also associated with significant change in HRQoL, but their incidence is low, compared to that of serious infection. These events are also likely to exceed the duration of treatment with any given therapy, makes their addition to the economic model complex. Furthermore, in the case of malignancies, a delayed onset creates uncertainty in identifying which part of the treatment sequences may have been associated with the adverse event. For these reasons, the impact of these AEs on HRQoL was explored only in a scenario analysis (see section B.3.8.3).

B.3.4.4 Health-related quality of life data used in the cost-effectiveness analysis

The utility values used in the cost-effectiveness analysis are summarised in Table 49; the utility values derived from AMAGINE-1 are generally consistent with those identified in the literature and in previous TAs (Table 48).

Table 49 Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Baseline	0.5206		B.3.4.1 (p123)	Derived from data collected in AMAGINE-1, based on patients with baseline PASI ≥ 12 and DLQI > 10, consistent with decision problem population
PASI < 50	0.016			
PASI 50–74	0.190			
PASI 75–89	0.295			
PASI 90–99	0.355			
PASI 100	0.368			
Serious infection	0.9858 (multiplier)		B.3.4.2 (p124)	Identified from literature (186)

PASI, Psoriasis Area Severity Index.

HRQoL was assumed to be constant over time in the analysis. Although EQ-5D population norms for the UK general population are shown to decline with age, survival is assumed to be equivalent across all treatments, therefore incorporating population norms in the model to inform baseline utility would not be expected to have any impact on the incremental results.

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

Identification of relevant cost and healthcare resource data is described in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

Cost and healthcare resource use inputs considered in the base-case analysis comprised drug acquisition and administration costs, monitoring costs, and costs associated with adverse events and BSC. Only direct medical costs were included in the model. Costs were sourced from 2015/16 NHS reference costs (142), Monthly Index of Medical Specialties (MIMS) (188), Personal Social Services Research Unit (PSSRU) (189) and published literature.

Treatment costs

Drug acquisition costs were derived from the online version of MIMS (188). Unit costs as well as trial and treatment period total costs for each comparator are summarised in Table 50. Total drug costs were estimated for the trial period and for each year of maintenance treatment. Drug costs for the period following the induction phase up to 1 year were estimated to account for differences between the frequency of doses in the first and subsequent years for some therapies.

A confidential simple discount patient access scheme (PAS) has been agreed and approved by Patient Access Scheme Liaison Unit (PASLU)/Department of Health and this price for brodalumab ([redacted] per dose) is used in the current analysis.

Ustekinumab was approved for use in patients with plaque psoriasis by NICE under a PAS in which the higher dose of 90 mg needed for people who weigh more than 100 kg was provided at the same total cost as the lower dose of 45 mg for people who weigh 100 kg or less. The PAS for the 90 mg dose of ustekinumab was included in the base case analysis. Apremilast, ixekizumab and secukinumab were recommended by NICE under a PAS that applied a confidential discount to their list prices. The base-case analysis uses the list price for these drugs.

Biosimilar etanercept and biosimilar infliximab are currently available in the UK. Biosimilar therapies and their branded counterparts have been assumed to be exchangeable in terms of efficacy and it was assumed that the NHS would give preference to the biosimilar drug over the originator for new patients with moderate-to-severe psoriasis. Therefore, the formulation with the lowest cost was used in the base-case analysis. More expensive options were explored in sensitivity analysis.

Etanercept 50 mg per week can be administered either as 25 mg twice weekly or 50 mg once weekly. The base-case analysis assumed that all patients would receive 50 mg once weekly; 25 mg twice weekly was used in a scenario analysis.

The dose for infliximab is weight-based: 5 mg/kg. A mean weight of 85.8 kg was calculated from the baseline data available from studies included in the NMA. Infliximab is only

available in 100 mg vials and vial-sharing between patients has been assumed not to occur. Thus, the cost of infliximab was based on the total number of vials necessary to administer the required dose and as such, includes wastage arising from the partial use of a vial. The alternative cost per milligram approach (no wastage) was used in a sensitivity analysis.

Both apremilast and DMF have a dose titration period, for which special titration medication packs are available. The induction phase costs for these comparators capture the up-titration of the drug and associated cost of the titration pack and then capture the usual daily dose and associated unit costs for non-titration packs of both medicines.

Table 50 Drug acquisition costs

Drug	Pack size	Dose (mg)	Pack cost	Cost per dose	Total cost (induction period)	Total cost (end of induction period to end of year 1)	Total annual cost (subsequent years)
Brodalumab (Kyntheum)	2	210	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab (Humira)	2	40	£704.28	£352.14	£3,521.40	£6,338.52	£9,155.64
Apremilast (Titration pack) [a]	690 mg		£256.18		£2,181.18	£4,954.91	£7,154.91
Apremilast [a]	56	30 BID	£550.00	£19.64			
Dimethyl fumarate (titration pack)	1,260 mg		£89.04		£1,023.96	£3,208.62	£4,633.26
Dimethyl fumarate	90	240 TID	£190.80	£12.72			
Etanercept 25 mg (Enbrel) [b]	4	25	£357.50	£89.38	£2,145.00	£7,150.00	£9,295.00
Etanercept 50 mg (Enbrel) [b]	4	50	£715.00	£178.75	£2,145.00	£7,150.00	£9,295.00
Biosimilar etanercept 50 mg (Benepali) [c]	4	50	£656.00	£164.00	£1,968.00	£6,560.00	£8,528.00
Infliximab (Remicade) [d]	1	100	£419.62	£2,098.10	£6,294.30	£10,490.50	£13,637.65
Infliximab (Flixabi) [d]	1	100	£377.00	£1,855.00	£5,655.00	£9,425.00	£12,252.50
Ixekizumab (Taltz) [a]	1	80	£1,125.00	£1,125.00	£7,875.00	£11,250.00	£14,625.00
Secukinumab (Cosentyx) [a]	1	300	£1,218.78	£1,218.78	£7,312.68	£12,187.80	£14,625.36
Ustekinumab 45 mg (Stelara)	1	45	£2,147.00	£2,147.00	£4,294.00	£6,441.00	£9,303.67
Ustekinumab 90 mg (Stelara) [e]	1	90	£2,147.00	£2,147.00	£4,294.00	£6,441.00	£9,303.67

[a] Apremilast, secukinumab and ixekizumab were recommended by NICE under a PAS that applied a confidential discount. The base-case analysis uses the list price for both drugs.
[b] Etanercept 50 mg per week can be administered either as 25 mg twice weekly or 50 mg once weekly. The base-case analysis assumed that all patients would receive 50 mg once weekly; 25 mg twice weekly was used in a scenario analysis.
[c] Biosimilar etanercept (Benepali) is currently available in the UK at a lower cost than the branded product, and was used in the base-case analysis. The more expensive option is explored in a scenario analysis.
[d] Infliximab dose based on a baseline weight of 85.8 kg and costs account for drug wastage at each administration.
[e] Ustekinumab was approved by NICE under a PAS in which the 90 mg dose for patients > 100 kg is provided at the same cost as the 45 mg dose for those ≤ 100 kg. This PAS price is used in the base-case analysis.

Administration costs

Brodalumab, adalimumab, etanercept, ixekizumab, secukinumab and ustekinumab are administered as a subcutaneous injection. All patients were assumed to be able to self-administer subcutaneous injections in the base case. This assumption reflects the expected zero cost to the NHS for injection support due to home-care and support schemes to be offered by LEO Pharma in line with other biologic manufacturers. Apremilast and dimethyl fumarate are given orally and require no resources for training or administration.

Infliximab is administered as an intravenous (IV) infusion by a health care professional. The cost of IV administration was based on the mean of a consultant- and a non-consultant led non-admitted face-to-face follow-up appointment. Unit costs were taken from 2015-16 NHS Reference Cost values (142) and estimated to be £96.48.

Monitoring costs

Resource use data associated with treatment monitoring were taken from recommendations in the BAD guideline for biologic interventions for psoriasis (29). These resources included regular outpatient visits and laboratory tests. Unit costs for each resource were obtained from 2015/16 NHS reference costs (142) and reported in Table 51. Frequency of monitoring and total cost during the trial and treatment period are reported in Table 52. Frequency of monitoring was assumed to be similar across treatments.

Table 51 Unit costs of treatment monitoring

Resource	Mean cost	Interquartile range	Reference
Outpatient attendance	£96.48	£73.39 to £116.20	NHS Reference Cost 2015-16, Outpatient attendance – Dermatology (330): WF01A & WF01A (142)
Full blood count	£3.10	£2.17 to £3.65	NHS Reference Cost 2015-16, DAPS05 (Haematology) (142)
Urea and electrolytes	£1.18	£0.78 to £1.39	NHS Reference Cost 2015-16, DAPS04 (Clinical biochemistry) (142)
Liver function tests	£1.18	£0.78 to £1.39	NHS Reference Cost 2015-16, DAPS04 (Clinical biochemistry) (142)

Table 52 Frequency and total cost of treatment monitoring during trial and treatment periods for each drug

	Induction period		Maintenance period (per year)	
Drug	Frequency	Total cost	Frequency	Total cost
Brodalumab, adalimumab, apremilast, dimethyl fumarate, etanercept, ixekizumab, secukinumab and ustekinumab	2	£203.89	2	£203.89
Infliximab	3	305.83	2	£203.89

Best supportive care

The cost of BSC was based on a retrospective observational study of 76 patients followed for 12 months prior to commencing biologics (Fonia *et al.,* 2010) (190), which has been recommended by NICE ERGs as the most plausible estimate of BSC resource use for the UK (71, 72, 159).

The annual cost of BSC (Table 53) was estimated from the sum of systemic medication costs and the cost of inpatient admissions and outpatient care. These costs comprise inpatient, intensive care unit and high dependency unit admissions; accident and emergency visits; outpatient visits; day ward admissions; and phototherapy and are assumed to reflect costs for how moderate-to-severe patients are managed in the absence of biologic treatment.

Costs were inflated from 2008 to 2017 prices using the health component of the Consumer Price Index from the Office for National Statistics (179). Inflated costs were converted to a 2-week cost and applied on each model cycle.

Table 53 Resource use and unit costs associated with BSC

Type of resource use	Annual cost	2-week cycle cost
Medication [a]	£1,570.29	£60.40
Inpatient admissions and outpatient care [b]	£3,712.82	£142.80
Total annual costs (2016–17)	£5,283.11	£203.20

[a] includes methotrexate, acitretin, ciclosporin, fumaric acid esters, hydroxycarbamide and mycophenolate mofetil.
[b] includes inpatient admissions, intensive care unit admissions, high dependency unit admissions, accident and emergency visits, outpatient visits, day ward admissions and phototherapy.

Costs for non-responders

Patients who fail to respond to biologics and switch to BSC may incur additional healthcare costs. According to 2015/16 NHS Hospital Episode Statistics (191), patients with a diagnosis of psoriasis vulgaris who received inpatient care have an average length of stay of 10.3 days at a cost of £448.72 per day. Because the resource use in Fonia *et al.* (190) included inpatient days, this cost was excluded from the base-case analysis to avoid overestimating inpatient care received by patients treated with BSC, but was explored in a scenario analysis (see section B.3.8.3).

B.3.5.2 Health state unit costs and resource use

Costs associated with each PASI response health state are presented in Table 54.

B.3.5.3 Adverse reaction unit costs and resource use

Serious infections were included in the base case analysis and were assumed to be serious enough to merit hospitalisation. The cost of a serious infection was considered to be a weighted average of six types of infection: sepsis, tuberculosis, pneumonia, skin and soft tissue infection, bone and joint infection and urinary tract infection. Weights were based on the number of finished consultant episodes described in the NHS reference costs for the

relevant Healthcare Resource Group (HRG). Costs associated with each adverse event were obtained from 2015/16 NHS reference costs (142).

Table 54 List of health states and associated costs in cost-effectiveness model

Health states	Item	Value	Reference
PASI < 50 PASI 50–74 PASI 75–89 PASI 90–99 PASI 100	*Treatment costs*		
	Brodalumab	[redacted] per dose	PAS Price
	Adalimumab	£352.14 per dose	MIMS, August 2017 (188)
	Apremilast	£19.64 per daily dose	
	Dimethyl Fumarate	£12.73 per daily dose	
	Etanercept	£164.00 per dose	
	Infliximab	£1,855.00 per dose	
	Ixekizumab	£1,125.00 per dose	
	Secukinumab	£1,218.78 per dose	
	Ustekinumab	£2,147.00 per dose	
	Administration costs		
	IV infusion	£96.48	NHS Reference Cost 2015–16, Outpatient attendance – Dermatology (330): WF01A & WF01A (142)
	Monitoring costs		
	Outpatient attendance	£96.48	NHS Reference Cost 2015–16, Outpatient attendance – Dermatology (330): WF01A & WF01A (142)
	Full blood count	£3.10	NHS Reference Cost 2015–16, DAPS05 (Haematology) (142)
	Urea and electrolytes	£1.18	NHS Reference Cost 2015–16, DAPS04 (Clinical biochemistry) (142)
	Liver function tests	£1.18	NHS Reference Cost 2015–16, DAPS04 (Clinical biochemistry) (142)
	BSC costs		
	Drug costs, inpatient and outpatient admissions	£5,283.11	Fonia *et al*. 2010 (190)

BSC, best supportive care; IV, intravenous; MIMS, Monthly Index of Medical Specialties; PAS, patient access scheme; PASI, Psoriasis Area Severity Index.

Table 55. Unit costs of treatment for adverse events

Adverse event	Adverse event sub-type	Unit cost	Mean cost	Source
Serious infection	Sepsis	£2,741.30	**£2,653.56**	NHS reference costs 2015/16: WJ06A-J (192)
	Tuberculosis	£3,872.88		NHS reference costs 2015/16: DZ14F-J (192)
	Pneumonia	£2,598.29		NHS reference costs 2015/16: DZ11K-V and DZ23H-N (192)
	Soft tissue infection	£1,964.55		NHS reference costs 2015/16: HD21D-H (192)
	Bone and joint infections	£4,777.47		NHS reference costs 2014/15: HD25-H (192)
	Urinary tract infection	£2,615.81		NHS reference costs 2015/16: LA04H-S (192)

B.3.5.4 Miscellaneous unit costs and resource use

No other healthcare resources were modelled in the analysis.

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

B.3.6.1 Summary of base-case analysis inputs

Table 56 Summary of variables applied in the economic model

	Variable	Value	CI (distribution)	Section in submission
Model settings	Discount rate (costs)	3.5%	Fixed (no sampling)	B.3.2.3 (p111)
	Discount rate (benefits)	3.5%	Fixed (no sampling)	
Patient characteristics	Age	45 years	Fixed (no sampling)	B.3.2.1 (p109)
	Weight	85.8 kg	Fixed (no sampling)	
	Male	68%	Fixed (no sampling)	
Baseline efficacy parameters, probit scale (median)	PASI 50	1.049	0.9461 to 1.151 (Coda)	B.3.3.1 (p118)
	PASI 75 cut-off	0.5275	0.5092 to 0.5463 (Coda)	
	PASI 90 cut-off	1.191	1.168 to 1.215 (Coda)	
	PASI 100 cut-off	1.985	1.955 to 2.014 (Coda)	
Treatment effects, probit scale (median)	BSC	0	Fixed	B.3.3.1 (p118); B.2.9.2, Figure 26 (p72)
	Brodalumab	[redacted]	[redacted]	
	Adalimumab	–1.988	–2.127 to –1.843 (Coda)	
	Apremilast	–0.9723	–1.123 to –0.8168 (Coda)	
	Etanercept	–1.3	–1.449 to –1.155 (Coda)	
	Infliximab	–2.388	–2.574 to –2.21 (coda)	
	Ixekizumab	–2.879	–3.023 to –2.738 (Coda)	
	Secukinumab	–2.555	–2.704 to –2.414 (Coda)	
	Ustekinumab	–2.128	–2.275 to –1.984 (Coda)	
	Dimethyl fumarate	–0.7092	–1.034 to –0.387 (Coda)	
Drop-out rate	All therapies	18.7%	Calculated by fitting exponential model to sampled values of drug survival at years 1, 2 and 3 (below)	B.3.3.1, Table 45 (p120)
First biologic drug survival	End year 1	77%	76% to 79% (Beta)	
	End year 2	63%	61% to 65% (Beta)	
	End year 3	53%	51% to 55% (Beta)	
Serious infection, rate	BSC	1.05%	0.75% to 1.43% (Beta)	B.3.3.1, Table 46 (121)
	Adalimumab	1.97%	1.61% to 2.39% (Beta)	
	Etanercept	1.47%	1.10% to 1.91% (Beta)	
	Infliximab	2.49%	1.88% to 3.23% (Beta)	
	Ustekinumab, Ixekizumab, Secukinumab	0.83%	0.61% to 1.09% (Beta)	
	Apremilast & dimethyl fumarate	1.28%	0.73% to 2.09% (Beta)	
Serious infection, rate ratio	Brodalumab vs ustekinumab	1.43	0.5 to 4.08 (Lognormal)	B.3.3.1, Table 46 (121)
Mortality, hazard ratio	Psoriasis vs general population	1.42	1.25 to 1.62 (Lognormal)	B.3.3.2 (p122)
EQ-5D (DLQI > 10)	Baseline	0.521	0.489 to 0.552	B.3.4.1, (p123)

	Variable	Value	CI (distribution)	Section in submission
Change from baseline EQ-5D (baseline adjusted, DLQI > 10)	PASI 0–49	0.016	Multivariate normal dist.	B.3.4.1, (p123)
	PASI 50–74	0.190	Multivariate normal dist.	
	PASI 75–89	0.295	Multivariate normal dist.	
	PASI 90–99	0.355	Multivariate normal dist.	
	PASI 100	0.368	Multivariate normal dist.	
Utility multiplier, adverse event	Serious infection	0.9858		B.3.4.2 (p124)
Drug costs (PAS price for brodalumab, list prices for other therapies)	Brodalumab	[redacted] per dose	Fixed (no sampling)	B.3.5.1, Table 50 (p129)
	Adalimumab	£352.14 per dose	Fixed (no sampling)	
	Apremilast	£19.64 per daily dose	Fixed (no sampling)	
	Dimethyl Fumarate	£12.73 per daily dose	Fixed (no sampling)	
	Etanercept	£164.00 per dose	Fixed (no sampling)	
	Infliximab	£1,855.00 per dose	Fixed (no sampling)	
	Ixekizumab	£1,125.00 per dose	Fixed (no sampling)	
	Secukinumab	£1,218.78 per dose	Fixed (no sampling)	
	Ustekinumab	£2,147.00 per dose	Fixed (no sampling)	
BSC cost	Inpatient admissions	£2,956.7	£1,469.45 to £4,443.95 (Lognormal)	Costs before inflation, B.3.5.1, Table 53 (p131)
	Medications	£1,250.5	£898.68 to £1,602.32 (Lognormal)	
Monitoring costs	Physician visit	£96.48	Weighted average of consultant and non-consultant led follow-up visit (see below)	B.3.5.1, Table 51 (p130)
	Full blood count (FBC)	£3.10	£2.17 to £3.65 (Gamma)	
	Urea and electrolytes (U&E)	£1.18	£0.78 to £1.39 (Gamma)	
	Liver function tests (LFT)	£1.18		
Physician visit	Consultant led, follow-up	£99.42	£76.43 to £119.65 (Gamma)	
	Non-consultant led, follow-up	£76.64	£52.88 to £92.97 (Gamma)	
Resource use: physician visits – induction period	All therapies except infliximab	2	Fixed (no sampling) [a]	B.3.5.1, Table 52 (p130)
	Infliximab	3	Fixed (no sampling) [a]	
Resource use: physician visits – maintenance period (annually)	All therapies except infliximab	2	Fixed (no sampling) [a]	B.3.5.1, Table 52 (p130)
	Infliximab	2	Fixed (no sampling) [a]	
Drug administration – infliximab	Cost of IV infusion	£96.48	Same as physician visit	B.3.4.2, Table 54 (p132)
	Number of IV infusions – induction period	3	Fixed (no sampling) [a]	B.3.5.1 (p128)
	Number of IV infusions – maintenance period (annually)	6.5	Fixed (no sampling) [a]	

	Variable	Value	CI (distribution)	Section in submission
Monitoring frequency – induction period	Number of FBC, LFT and U&E - all therapies except infliximab	2	Fixed (no sampling) [a]	B.3.5.1, Table 52 (p130)
	Number of FBC, LFT and U&E – Infliximab	3	Fixed (no sampling) [a]	
Monitoring frequency – maintenance period (annually)	Number of FBC, LFT and U&E – all therapies except infliximab	2	Fixed (no sampling) [a]	B.3.5.1, Table 52 (p130)
	Number of FBC, LFT and U&E – infliximab	2	Fixed (no sampling) [a]	

BSC, best supportive care; CI, confidence interval; dist, distribution; FBC, full blood count; IV, intravenous; LFT, liver function test; PASI, Psoriasis Area Severity Index; U&E, urea and electrolytes.
[a] Unit costs were sampled instead

B.3.6.2 Assumptions

Table 57 Assumptions in the economic model

Parameter	Assumptions	Consistent with prior TAs?	Justification
Time horizon	40 years	Yes [a]	40 years is sufficient to capture all relevant costs and benefits of comparator sequences.
Health states	Defined by PASI response	Yes	PASI response was used as a primary endpoint in the trials and is considered the standard measure of psoriasis in clinical practice.
Treatment efficacy	PASI response achieved during induction is maintained during maintenance	Yes	Registry data suggested that the biggest driver of long-term discontinuation is loss of response. In the absence of long-term evidence of PASI level maintenance for all of the comparators in the model, and to ensure patient parsimony, it was assumed that loss of PASI response would happen at discontinuation.
	PASI response is not affected by prior treatments in a sequence	Yes	Results of subgroup analyses from the AMAGINE trials showed that the efficacy of brodalumab was similar in patients with and without exposure to prior therapies, a finding that is similar to evidence presented in previous TAs of psoriasis treatments.
Mortality	For completeness, all-cause mortality was applied in the model and was assumed to be higher among patients with moderate-to-severe psoriasis than the general population; no treatment effect on mortality was assumed	No	Evidence suggested that patients with moderate-to-severe psoriasis face an increased risk of death relative to matched controls; however, there was no evidence to indicate that treatment has an effect on mortality.
Dis-continuation	All-cause discontinuation occurred at a constant rate. No treatment effect was assumed for treatment discontinuation	Yes	UK registry data have shown that psoriasis patients on biologic therapies discontinue treatment over time. Evidence is mixed as to whether drug survival is different between therapies and whether it is different for first, second or later line treatments.
Adverse events	Serious infections were included in the base-case	Yes [b]	Costs and HRQoL were adjusted for serious infections, the rates of which were calculated from a combination of sources, including a large psoriasis registry (PSOLAR) and long-term RCTs.

[a] Some previous TAs have used a 10-year time horizon. However, a longer time horizon is needed to capture all relevant costs and benefits of treatment sequences; the ixekizumab submission used a lifetime horizon (72).
[b] Costs associated with adverse events were included in the base-case analysis of the TA submission for secukinumab (71), and were included as a scenario analysis in the ixekizumab submission (72).
HRQoL, health-related quality of life; PASI, Psoriasis Area Severity Index; TA, technology appraisal.

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

Clinical outcomes from the model and disaggregated results of the base-case incremental cost-effectiveness analysis are presented in Appendix J.

A summary of base case cost-effectiveness results is presented in Table 58. ICERs are presented for a fully incremental analysis and for pairwise analyses of the brodalumab sequence versus each comparator sequence.

In the fully incremental analysis, DMF (sequence 9), which was associated with the lowest total QALYs at the lowest cost, is the referent comparator. Brodalumab (sequence 1) is the first comparator sequence on the cost-effectiveness frontier and is associated with an ICER of £13,353 per QALY versus DMF (sequence 9). Ixekizumab (sequence 6) is most costly and generates 0.031 more QALYs than brodalumab (sequence 1), with an ICER of £894,010 per QALY. The other comparators are dominated or extendedly dominated.

Compared with DMF, apremilast, etanercept, adalimumab, ustekinumab, secukinumab and infliximab, brodalumab 210 mg Q2W is associated with more QALYs. When compared pairwise to each treatment sequence, brodalumab (sequence 1) is associated with ICERs ranging from £7,145 versus etanercept (sequence 4) to £13,353 versus DMF (sequence 9) . Brodalumab (sequence 1) dominates infliximab (sequence 5), secukinumab (sequence 7), ustekinumab (sequence 8) and adalimumab (sequence 2), providing more QALYs at a lower cost.

Table 58 Base-case results

Sequence	1st line	2nd line	3rd line	4th line	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) fully incremental	ICER (£/QALY): BRO sequence vs comparator
9	DMF	UST	SEC	BSC	£146,101	18.76	12.64	£0	0	0	-	£13,353
3	APR	UST	SEC	BSC	£149,236	18.76	12.72	£3,136	0	0.07	Extendedly dominated	£9,955
4	ETN	UST	SEC	BSC	£151,791	18.76	12.82	£5,690	0	0.18	Extendedly dominated	£7,145
2	ADA	UST	SEC	BSC	£156,036	18.76	13.10	£9,935	0	0.46	Dominated	Dominated
8	UST	ADA	SEC	BSC	£156,156	18.76	13.10	£10,055	0	0.46	Dominated	Dominated
7	SEC	UST	ADA	BSC	£161,524	18.76	13.11	£15,423	0	0.47	Dominated	Dominated
5	INF	UST	SEC	BSC	£172,212	18.76	13.23	£26,111	0	0.59	Dominated	Dominated
1	BRO	UST	SEC	BSC	£155,517	18.76	13.35	£9,416	0	0.71	£13,353	N/A
6	IXE	UST	SEC	BSC	£182,957	18.76	13.38	£36,857	0	0.74	£894,010	£894,010

ADA, adalimumab; APR, apremilast; BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ETN, etanercept 50 mg per week; ICER, incremental cost-effectiveness ratio; INF, infliximab; IXE, ixekizumab; LYG, life years gained; QALYs, quality-adjusted life years; SEC, secukinumab; UST, ustekinumab.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity (PSA) analysis was undertaken with 1,000 model simulations. A full list of all parameters included in the PSA is presented in section B.3.6.1, Table 56. Probability distributions were based on 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 is assumed to be equal to 20% of the mean.

Uncertainty in the probabilities of PASI response were obtained directly from the joint posterior distributions of the NMA. Beta distributions were used for other probabilities, gamma distributions were used for NHS reference costs, and lognormal distributions were used for treatment effects such as odd ratios. A multivariate normal distribution was used for utilities. Table 59 presents the variance-covariance matrix used to preserve correlations between parameters in the regression model.

Table 59 Variance – covariance matrix from EQ-5D regression model

PASI change category	Intercept	PASI 100	PASI 50–74	PASI 75–89	PASI 90–99	PASI 0–49	Baseline DLQI
	0.000707						
PASI 100	–0.0003	0.000776					
PASI 50–74	–0.00023	0.000283	0.001677				
PASI 75–89	–0.00027	0.000284	0.000287	0.00128			
PASI 90–99	–0.00025	0.000284	0.000289	0.000286	0.000973		
PASI 0–49							
Baseline DLQI	–0.00003	1.25E-06	-4.02E-06	-1.13E-06	-2.29E-06		2.24E-06

A summary of the probabilistic results is presented in Table 60. DMF (sequence 9) is the referent treatment, with lowest costs and QALYs. Brodalumab (sequence 1) has an ICER of £13,202 compared to DMF (sequence 9), extendedly dominates apremilast (sequence 3) and etanercept (sequence 4) and dominates adalimumab (sequence 2), ustekinumab (sequence 8), secukinumab (sequence 7) and infliximab (sequence 5). Ixekizumab (sequence 6) is associated with an ICER of £903,712 when compared to brodalumab (sequence 1).

A graphical depiction of the simulations is presented in Figure 30, and the cost-effectiveness acceptability curve is presented in Figure 31. Brodalumab (sequence 1) and DMF (sequence 9) are the treatment sequences with the greatest probabilities of being cost-effective over a range of willingness-to-pay thresholds: 0 to £13,000 for dimethyl fumarate (sequence 9) and over £14,000 for brodalumab (sequence 1).

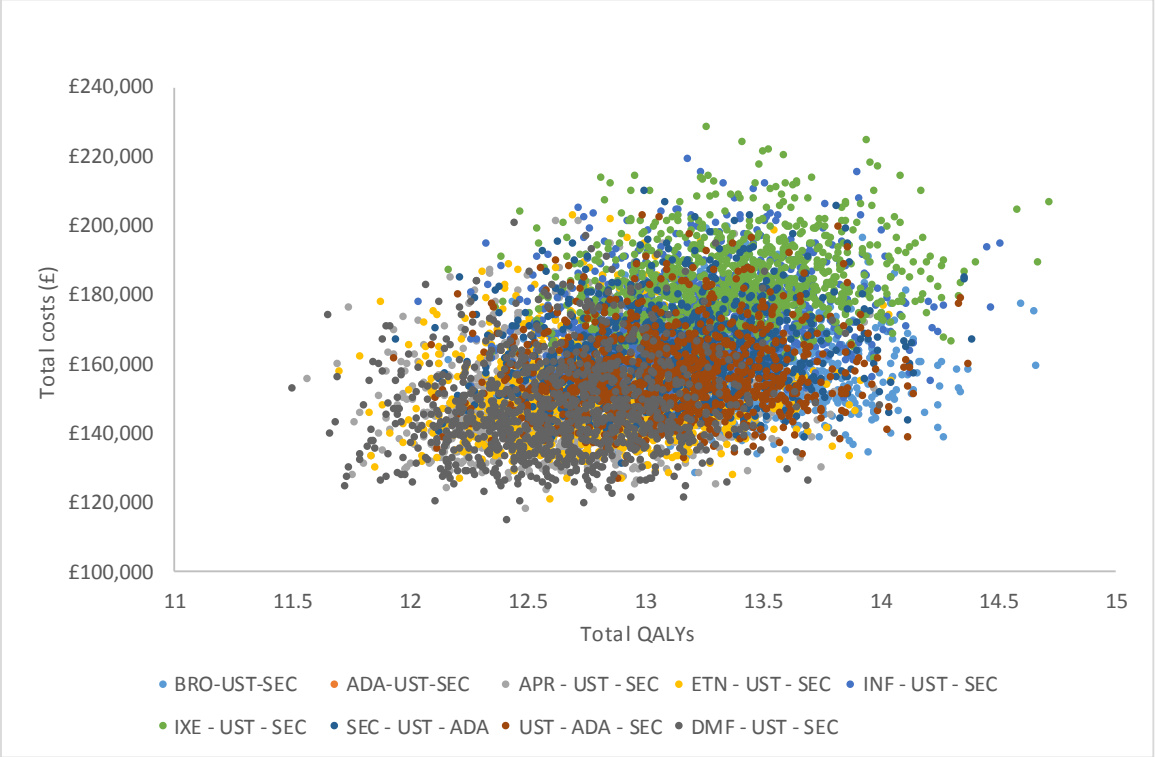
Given a willingness-to-pay threshold of £20,000 per QALY gained, brodalumab has the highest probability of being cost-effective (96%), followed by DMF (4%). At £30,000, brodalumab (sequence 1) has a 100% probability of being the most cost-effective of the modelled sequences.

Table 60 Results of probabilistic sensitivity analysis

Comparator	Total QALYs		Total costs		ICER (£/QALY) fully incremental	ICER (£/QALY): BRO sequence vs comparator
	Mean	95% CrI	Mean	95% CrI		
9: DMF	12.65	11.9 to 13.43	£146,710	£126,074 to £179,277	-	£13,202
3: Apremilast	12.72	11.98 to 13.49	£149,869	£129,584 to £181,444	Extendedly dominated	£9,678
4: Etanercept	12.83	12.09 to 13.61	£152,392	£132,811 to £182,978	Extendedly dominated	£6,879
2: Adalimumab	13.11	12.39 to 13.86	£156,499	£137,975 to £184,785	Dominated	Dominated
8: Ustekinumab	13.11	12.39 to 13.86	£156,632	£138,094 to £184,930	Dominated	Dominated
7: Secukinumab	13.12	12.4 to 13.88	£162,055	£142,929 to £190,655	Dominated	Dominated
5: Infliximab	13.24	12.52 to 13.99	£172,646	£153,935 to £201,295	Dominated	Dominated
1: Brodalumab	13.35	12.63 to 14.10	£155,966	£138,637 to £182,568	£13,202	N/A
6: Ixekizumab	13.38	12.67 to 14.15	£183,489	£165,010 to £210,252	£903,712	£903,712

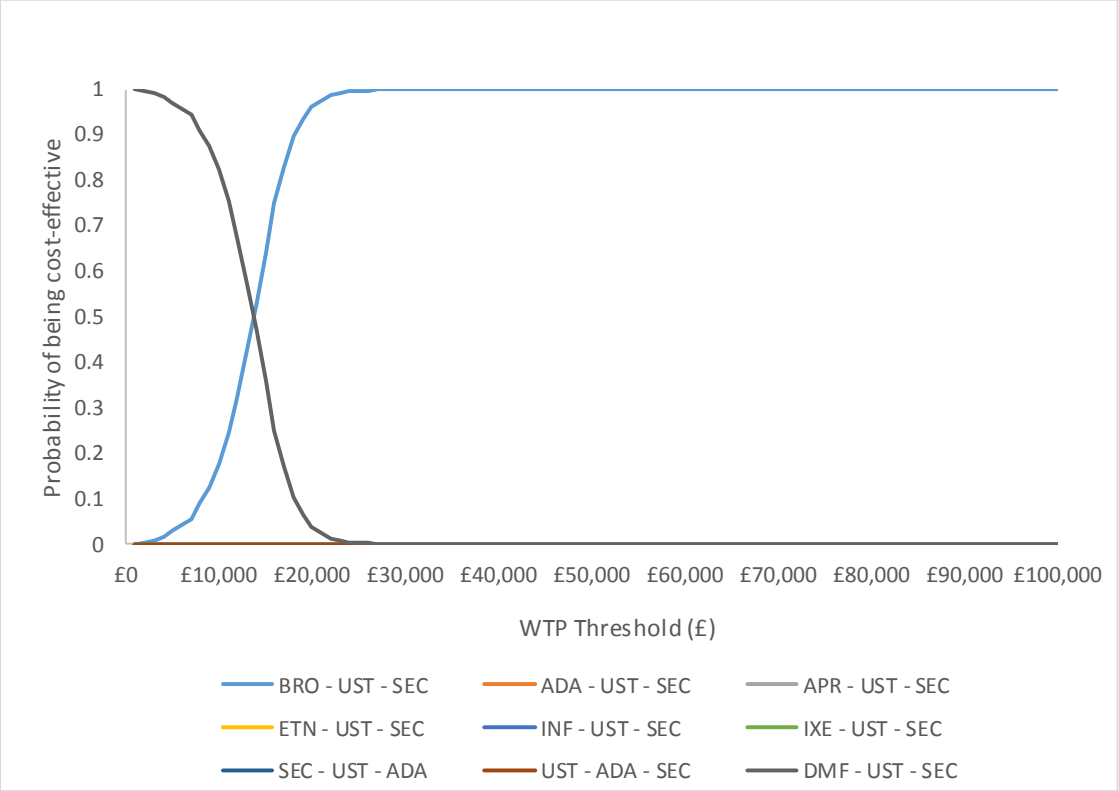
BRO, brodalumab; BSC, best supportive care; CrI, credible interval; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year.

Figure 30 PSA Scatterplot on cost-effectiveness plane



ADA, adalimumab; APR, apremilast; BRO, brodalumab; DMF, dimethyl fumarate; ETN, etanercept 50 mg per week; INF, infliximab; IXE, ixekizumab; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; SEC, secukinumab; UST, ustekinumab.

Figure 31 Cost-effectiveness acceptability curve



ADA, adalimumab; APR, apremilast; BRO, brodalumab; DMF, dimethyl fumarate; ETN, etanercept 50 mg per week; INF, infliximab; IXE, ixekizumab; SEC, secukinumab; UST, ustekinumab; WTP, willingness-to-pay.

B.3.8.2 Deterministic sensitivity analysis

One-way sensitivity analyses (OWSA) were undertaken to assess the impact of key variables on the model outcomes (Table 61). The annual cost of BSC was varied between the upper and lower limits of the 95% confidence interval from Fonia *et al*. 2010 (190) and the efficacy of BSC, brodalumab and other comparators was varied between the upper and lower limits of the 95% credible intervals from the NMA. The annual discontinuation rate as well as costs for all drugs were varied by 20% of the mean.

Table 61 Inputs for one-way sensitivity analysis

Parameter		Mean	Lower bound	Upper bound	Comment
Annual discontinuation rate		18.7%	14.9%	22.4%	± 20% of mean
Annual cost of BSC		£4,207	£2,368	£6,046	95% CI of values in Fonia *et al.* 2010 (190)
BSC efficacy (PASI 50, 75, 90, 100)		15%, 6%, 1%, 0%	12%, 5%, 1%, 0%	17%, 7%, 2%, 0%	95% CrI NMA
Brodalumab efficacy, treatment effect vs placebo [a]		[redacted]	[redacted]	[redacted]	95% CrI NMA
Comparator effect vs placebo [a]	Adalimumab	–1.988	–2.127	to –1.843	95% CrI NMA
	Apremilast	–0.9723	–1.123	–0.8168	95% CrI NMA
	Etanercept	–1.3	–1.449	–1.155	95% CrI NMA
	Infliximab	–2.388	–2.574	–2.21	95% CrI NMA
	Ixekizumab	–2.879	–3.023	–2.738	95% CrI NMA
	Secukinumab	–2.555	–2.704	–2.414	95% CrI NMA
	Ustekinumab	–2.128	–2.275	–1.984	95% CrI NMA
	DMF	–0.7092	–1.034	–0.387	95% CrI NMA
Brodalumab price per dose [b]		[redacted]	[redacted]	[redacted]	± 20% of mean
Comparator price per dose	Adalimumab	£352.14	278.71	£422.57	± 20% of mean
	Apremilast	£19.64	7.86	£11.79	± 20% of mean
	DMF	£12.73	1.70	£2.54	± 20% of mean
	Etanercept	£164.00	£131.20	£196.80	± 20% of mean
	Infliximab	£1,855.00	£301.60	£452.40	± 20% of mean
	Ixekizumab	£1,125.00	£900.00	£1350.00	± 20% of mean
	Secukinumab	£1,218.78	£975.02	£1,462.40	± 20% of mean
	Ustekinumab	£2,147.00	£1,717.60	£2,576.40	± 20% of mean

[a] treatment effect on probit scale.
[b] PAS price.
CI, confidence interval; CrI, credible interval; DMF, dimethyl fumarate; NMA, network meta-analysis; PAS, patient access scheme.

The tornado diagrams in Figure 32 show the variation in base-case model results from OWSA (brodalumab versus comparator). For the pairwise comparisons in which brodalumab does not dominate the comparator (i.e. vs DMF and adalimumab), ICER-based tornado diagrams are presented. For the remaining comparisons in which brodalumab either dominates the comparator or where it is less costly and less effective, incremental net benefit (INB) based diagrams are presented.

The main driver of the ICER/INB across pairwise comparisons is the acquisition cost of brodalumab and of the comparator therapy. The cost of BSC has an impact in the comparisons of brodalumab with DMF, apremilast, and secukinumab, but was less significant in the other comparisons. The effect of varying the efficacy of the comparator was largest in the comparison with DMF. The annual discontinuation rate had an impact on the comparisons of brodalumab with apremilast, etanercept, secukinumab, infliximab and ixekizumab.

Figure 32 OWSA results

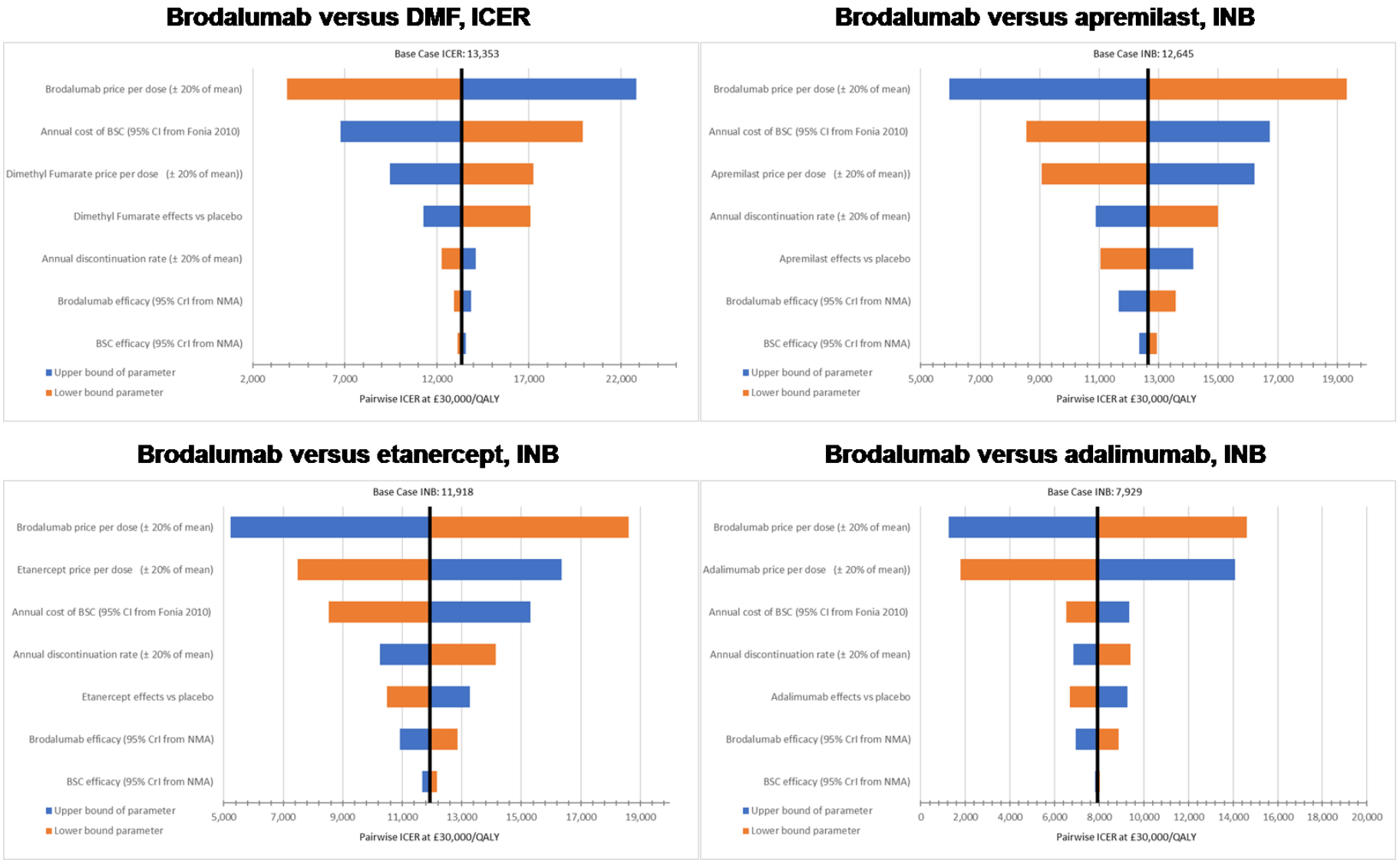
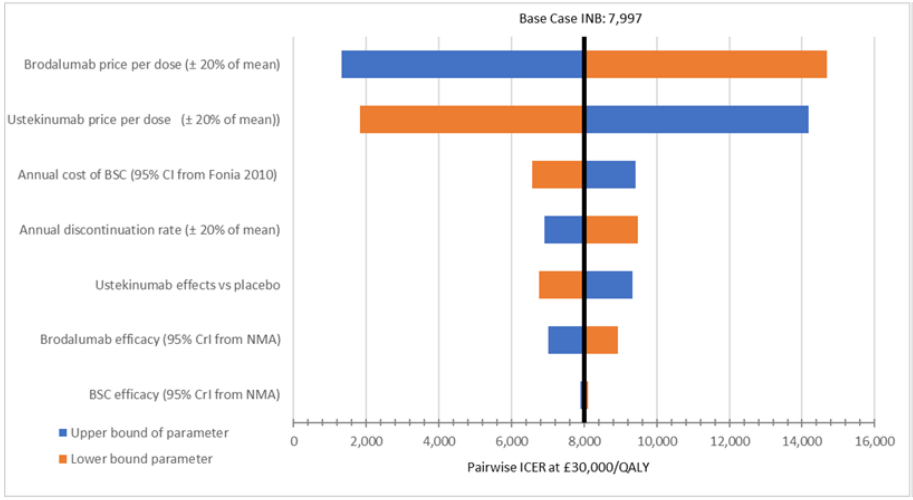
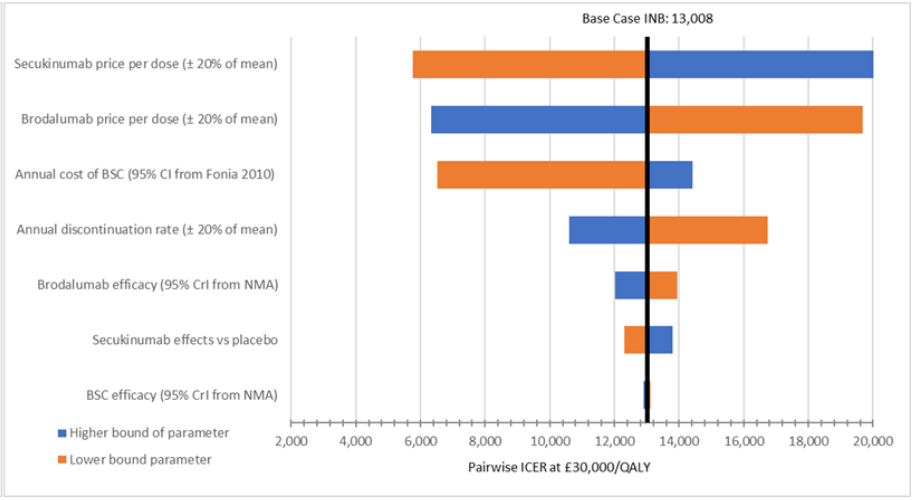


Figure 32 (continued) **OWSA results**

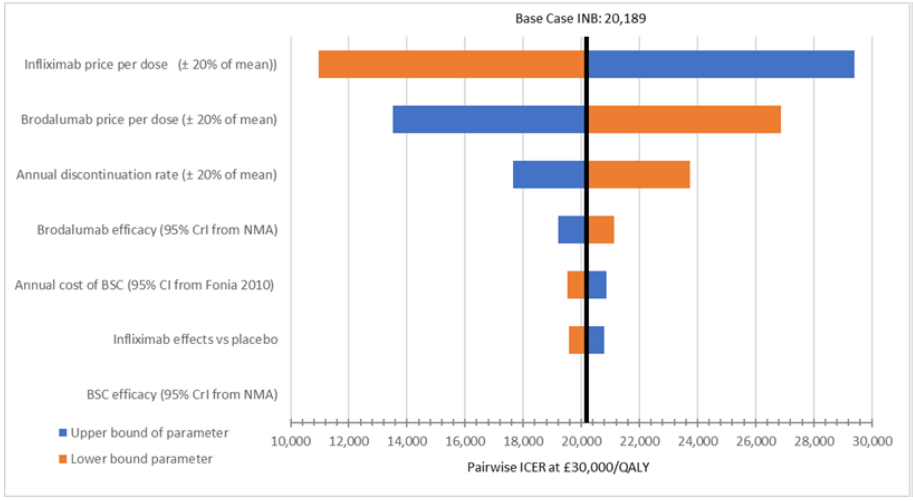
Brodalumab versus ustekinumab, INB



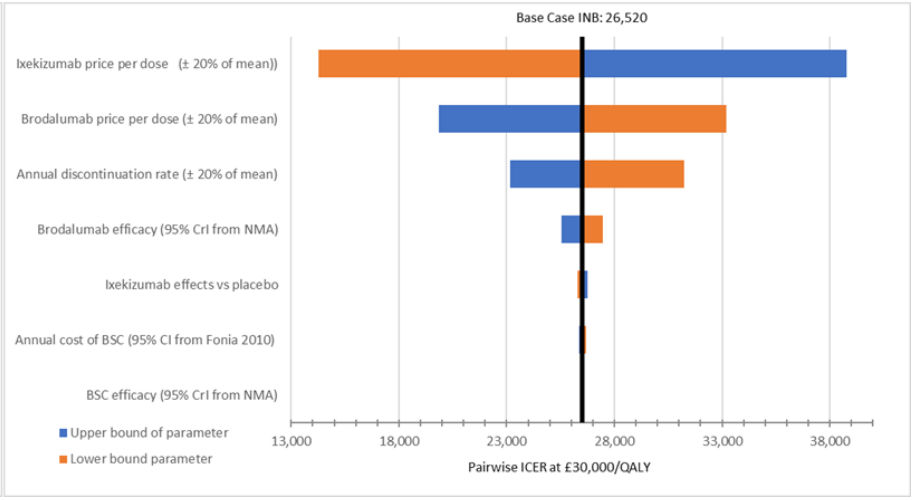
Brodalumab versus secukinumab, INB



Brodalumab versus infliximab, INB



Brodalumab versus ixekizumab, INB



B.3.8.3 Scenario analyses

Structural uncertainty was explored by generating results using alternative assumptions for key input parameters. Each scenario is described in further detail below.

Scenario 1: single treatment comparator

A fully incremental analysis was undertaken using treatment with each of the comparators followed immediately by BSC. In this analysis BSC on its own was also included as a comparator. The results of this scenario are presented in Table 62. DMF as a single treatment dominated BSC. Brodalumab was the next strategy on the cost-effectiveness frontier with an ICER of £16,451 vs DMF and was less costly and slightly less effective than ixekizumab, which had an ICER of £733,988. When compared in a pairwise fashion, the ICER for brodalumab as a single comparator ranged from £3,805 versus adalimumab to £16,451 versus DMF. Brodalumab dominated ustekinumab, infliximab and secukinumab.

Table 62 Results of scenario 1: single treatment comparator

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
BSC	10.67	£99,637	0.00	£0	Dominated	£12,540
DMF	10.90	£98,899	0.23	−£737	−£3,277	£16,451
Apremilast	10.99	£102,696	0.32	£3,060	Extendedly dominated	£13,773
Etanercept	11.13	£106,087	0.46	£6,451	Extendedly dominated	£11,598
Adalimumab	11.50	£112,695	0.83	£13,058	Extendedly dominated	£3,805
Ustekinumab	11.57	£114,617	0.90	£14,981	Dominated	Dominated
Infliximab	11.66	£129,759	0.99	£30,122	Dominated	Dominated
Secukinumab	11.74	£139,036	1.07	£39,400	Dominated	Dominated
Brodalumab	11.81	£113,873	1.14	£14,236	£16,451	N/A
Ixekizumab	11.84	£141,502	1.17	£41,865	£733,988	£733,988

BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year

Scenario 2: Infliximab as common 3rd line therapy

Infliximab was tested as an alternative 3rd line therapy across the sequences, replacing secukinumab. NICE recommends infliximab only in patients with very severe disease, and although the model assumes no disease progression, it is in this scenario assumed that patients who have failed two previous lines of therapy would receive infliximab. This is also consistent with the ixekizumab TA submission (145).

The results of this scenario (Table 63) were similar to the base-case analysis.

Table 63 Results of scenario 2: infliximab as common 3rd line therapy

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
9: DMF	12.58	£138,361	0.00	£0	-	£14,505
3: Apremilast	12.65	£141,607	0.08	£3,245	Extendedly dominated	£11,125
4: Etanercept	12.76	£144,300	0.19	£5,939	Extendedly dominated	£8,348
2: Adalimumab	13.04	£148,938	0.46	£10,576	Dominated	Dominated
8: Ustekinumab	13.04	£149,058	0.47	£10,697	Dominated	Dominated
7: Secukinumab	13.05	£152,477	0.47	£14,116	Dominated	Dominated
5: Infliximab [a]	13.23	£174,174	0.66	£35,813	Dominated	Dominated
1: Brodalumab	13.29	£148,701	0.71	£10,340	£14,505	N/A
6: Ixekizumab	13.32	£176,173	0.74	£37,812	£887,502	£887,502

[a] For consistency with the approach taken in the base-case analysis, where secukinumab was the common 3rd line therapy, in this scenario the infliximab treatment sequence was infliximab – ustekinumab – adalimumab – BSC.
BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year

Scenario 3: 10-year time horizon

A time horizon of 10 years was tested in a scenario analysis with the same treatment sequences as the base-case analysis. This brings this model into alignment with time horizons used in earlier submission in psoriasis, though many did not use sequences.

DMF (sequence 9) was the referent comparator sequence in the fully incremental analysis (Table 64). Brodalumab (sequence 1) was the first comparator sequence on the cost-effectiveness frontier and was associated with an ICER of £7,067 vs DMF (sequence 9). Ixekizumab (sequence 6) was the most costly sequence, generating 0.021 more QALYs than the brodalumab sequence with an ICER of £1,215,357.

When compared pairwise to each treatment sequence, brodalumab (sequence 1) is associated with ICERs ranging from £1,967 versus apremilast (sequence 3) to £7,067 versus DMF (sequence 9). Brodalumab (sequence 1) dominates etanercept (sequence 4), adalimumab (sequence 2), ustekinumab (sequence 8), infliximab (sequence 5) and secukinumab (sequence 7).

Table 64 Results of scenario 3: 10-year time horizon

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
9: DMF	6.33	£80,420	0.00	£0	-	£7,067
3: Apremilast	6.37	£82,698	0.04	£2,278	Extendedly dominated	£1,967
4: Etanercept	6.44	£84,169	0.11	£3,749	Dominated	Dominated
2: Adalimumab	6.60	£85,724	0.27	£5,304	Dominated	Dominated
8: Ustekinumab	6.60	£85,920	0.27	£5,500	Dominated	Dominated
7: Secukinumab	6.62	£96,113	0.30	£15,693	Dominated	Dominated
5: Infliximab	6.68	£99,825	0.35	£19,405	Dominated	Dominated
1: Brodalumab	6.76	£83,460	0.43	£3,040	£7,067	N/A
6: Ixekizumab	6.78	£108,756	0.45	£28,336	£1,215,357	£1,215,357

BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year

Scenario 4: effect modification

There was uncertainty regarding the effect that previous exposure to biological therapies may have on probabilities of primary response as well as rates of secondary non-response. To account for a potential reduced efficacy among patients with previous exposure to biological therapies, an effect modifier from a Danish registry study was applied (34). Gniadecki *et al.* (2015) found prior (primary or secondary) failure of biologic treatment to be a significant predictor of quicker time to discontinuation. The authors report an odds ratio of 1.24, calculated using a forward Wald method on data from a Cox regression model. This value, 1.24, was used in three scenarios: A) it was used to adjust the probabilities of primary response during induction (by dividing each level of PASI response by 1.24); B) it was applied to the annual discontinuation rate, thus increasing the rate of drop-outs for people with prior exposure (22% annually for 2nd and 3rd line drugs compared to 18.7% for 1st line); and C) the first two scenarios were combined, with the effect modifier applied to both primary and secondary failures.

DMF (sequence 9) was the referent comparator sequence in the fully incremental analyses of scenarios A, B and C (Table 65). Brodalumab (sequence 1) was the next sequence on the cost-effectiveness frontier, with an ICER versus DMF of £13,854, £13,755 and £14,158 in scenarios A, B and C, respectively. In the fully incremental analysis, brodalumab (sequence 1) extendedly dominated apremilast (sequence 3) and etanercept (sequence 4) and dominated adalimumab (sequence 2), ustekinumab (sequence 8), infliximab (sequence 5) and secukinumab (sequence 7) in all three scenarios. Ixekizumab (sequence 6) was more effective and more costly, with ICERs versus brodalumab (sequence 1) ranging from £840,056 in scenario C to £866,682 in scenario B.

Results of pairwise comparisons with brodalumab were similar to the base case.

Table 65 Results of scenario 4: effect modification

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
A) Effect modification on induction phase response only						
9: DMF	12.34	£139,227	0	0	-	£13,854
3: Apremilast	12.42	£142,464	0.08	£3,237	Extendedly dominated	£10,610
4: Etanercept	12.54	£145,146	0.19	£5,919	Extendedly dominated	£7,936
2: Adalimumab	12.83	£149,752	0.48	£10,525	Dominated	Dominated
8: Ustekinumab	12.84	£150,037	0.50	£10,810	Dominated	Dominated
7: Secukinumab	12.88	£158,172	0.54	£18,945	Dominated	Dominated
5: Infliximab	12.96	£166,064	0.62	£26,836	Dominated	Dominated
1: Brodalumab	13.09	£149,492	0.74	£10,265	£13,854	N/A
6: Ixekizumab	13.12	£176,962	0.77	£37,734	£860,923	£860,923
B) Effect modification on long-term discontinuation only						
9: DMF	12.41	£140,951	0	0	-	£13,755
3: Apremilast	12.49	£144,169	0.08	£3,217	Extendedly dominated	£10,485
4: Etanercept	12.61	£146,827	0.19	£5,876	Extendedly dominated	£7,787
2: Adalimumab	12.89	£151,364	0.48	£10,412	Dominated	Dominated
8: Ustekinumab	12.90	£151,608	0.49	£10,656	Dominated	Dominated
7: Secukinumab	12.94	£158,980	0.52	£18,028	Dominated	Dominated
5: Infliximab	13.03	£167,650	0.61	£26,698	Dominated	Dominated
1: Brodalumab	13.15	£151,055	0.73	£10,103	£13,755	N/A
6: Ixekizumab	13.18	£178,519	0.77	£37,567	£866,682	£866,682
C) Effect modification on both induction phase response and long-term discontinuation						
9: DMF	12.16	£134,906	0	0	-	£14,158
3: Apremilast	12.24	£138,210	0.08	£3,304	Extendedly dominated	£11,011
4: Etanercept	12.36	£140,978	0.20	£6,072	Extendedly dominated	£8,421
2: Adalimumab	12.66	£145,824	0.50	£10,918	Dominated	Dominated
8: Ustekinumab	12.68	£146,221	0.52	£11,315	Dominated	Dominated
7: Secukinumab	12.73	£156,068	0.58	£21,162	Dominated	Dominated
5: Infliximab	12.80	£162,226	0.64	£27,320	Dominated	Dominated
1: Brodalumab	12.92	£145,737	0.77	£10,831	£14,158	N/A
6: Ixekizumab	12.95	£173,226	0.80	£38,320	£840,056	£840,056

BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year

Scenario 5: discontinuation rates by drug class

In the base case, all drugs were assumed to have the same discontinuation rate during maintenance treatment (see section B.3.3.1). In this scenario, anti-TNFs and IL-inhibitors are assumed to differ in their rates of discontinuation, with IL-inhibitors expected to have longer drug survival than anti-TNFs.

As in the base-case analysis, DMF (sequence 9) was the referent comparator sequence in the fully incremental analysis (Table 66). In this scenario, brodalumab (sequence 1) was next on the frontier with an ICER of £3,495 versus DMF (sequence 9). Ixekizumab (sequence 6) was the most costly sequence, generating 0.045 more QALYs than the brodalumab sequence with an ICER of £1,118,334. Brodalumab dominated secukinumab, infliximab, ustekinumab and the anti-TNFs.

Table 66 Results of scenario 5: discontinuation rates by drug class

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
9: DMF	14.05	£174,624	0.00	£0	-	£3,495
3: Apremilast	14.11	£177,523	0.06	£2,899	Extendedly dominated	£551
4: Etanercept	14.20	£179,673	0.15	£5,049	Dominated	Dominated
2: Adalimumab	14.43	£182,169	0.37	£7,545	Dominated	Dominated
8: Ustekinumab	14.43	£182,288	0.38	£7,664	Dominated	Dominated
7: Secukinumab	14.47	£199,865	0.41	£25,241	Dominated	Dominated
5: Infliximab	14.54	£200,541	0.49	£25,917	Dominated	Dominated
1: Brodalumab	15.03	£178,028	0.97	£3,404	£3,495	N/A
6: Ixekizumab	15.07	£228,714	1.02	£54,090	£1,118,334	£1,118,334

BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year

Scenario 6: branded prices for etanercept and infliximab

In this scenario, the higher branded prices of etanercept and infliximab were used. Because these therapies were dominated or extendedly dominated in the base case, using higher prices leaves the results of the fully incremental analysis unchanged. In the pairwise analysis, brodalumab (sequence 1) has a lower ICER versus etanercept (sequence 4), than in the base case (£4,469 vs £7,145), and infliximab is still dominated (Table 67).

Table 67 Results of scenario 6: branded prices for etanercept and infliximab

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
9: DMF	12.64	£146,101	0.00	£0	-	£13,353
3: Apremilast	12.72	£149,236	0.07	£3,136	Extendedly dominated	£9,955
4: Etanercept	12.82	£153,186	0.18	£7,085	Extendedly dominated	£4,469
2: Adalimumab	13.10	£156,036	0.46	£9,935	Dominated	Dominated
8: Ustekinumab	13.10	£156,156	0.46	£10,055	Dominated	Dominated
7: Secukinumab	13.11	£161,524	0.47	£15,423	Dominated	Dominated
5: Infliximab	13.23	£177,272	0.59	£31,172	Dominated	Dominated
1: Brodalumab	13.35	£155,517	0.71	£9,416	£13,353	N/A
6: Ixekizumab	13.38	£182,957	0.74	£36,857	£894,010	£894,010

BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year

Scenario 7: Cost of infliximab excluding wastage

In this scenario, the cost for infliximab was calculated based on the total weight-based dose in milligrams (429 mg) multiplied by its cost per milligram (£3.77). Using this costing method, the first year and subsequent year drug costs for infliximab are £12,939 and £10,513 (compared with £15,080 and £12,252 in the base case), respectively.

Although the total cost of the infliximab sequence was reduced, results of both the fully incremental analysis and pairwise comparison with brodalumab are unchanged from the base case because infliximab is still dominated (Table 68).

Table 68 Results of scenario 7: cost of infliximab excluding wastage

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
9: DMF	12.64	£146,101	0.00	£0	-	£13,353
3: Apremilast	12.72	£149,236	0.07	£3,136	Extendedly dominated	£9,955
4: Etanercept	12.82	£151,791	0.18	£5,690	Extendedly dominated	£7,145
2: Adalimumab	13.10	£156,036	0.46	£9,935	Dominated	Dominated
8: Ustekinumab	13.10	£156,156	0.46	£10,055	Dominated	Dominated
7: Secukinumab	13.11	£161,524	0.47	£15,423	Dominated	Dominated
5: Infliximab	13.23	£165,855	0.59	£19,754	Dominated	Dominated
1: Brodalumab	13.35	£155,517	0.71	£9,416	£13,353	N/A
6: Ixekizumab	13.38	£182,957	0.74	£36,857	£894,010	£894,010

BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year

Scenario 8: alternative sources of utility data

In this scenario, alternative sources of utility data were explored. First, utility data from all patients in AMAGINE-1 were used, rather than data from patients with baseline DLQI > 10 as in the base-case analysis (see section B.3.4.1). Second, PASI response state-specific utility gains were sourced from previous submissions of biologic therapies in the treatment of moderate-to-severe psoriasis (see Table 69).

Compared with the base-case analysis, the use of alternative utility data reduced the difference in QALYs gained between the most- and least effective therapies, but the ranking of therapies was unchanged (Table 70).

Table 69 Utility data used in scenario analysis 8

Source	PASI 00	PASI 50	PASI 75	PASI 90	PASI 100
A) AMAGINE-1 all patients	0.004	0.135	0.244	0.280	0.290
B) York 4th Quartile DLQI (148)	0.12	0.29	0.38	0.41	0.41
C) Secukinumab submission, patients with DLQI > 10 (71)	0.109	0.193	0.226	0.264	0.264
D) Median values in previous STAs (Table 48)	0.063	0.178	0.22	0.264	0.264

DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; STA, Single Technology Appraisal.

Table 70 Results of scenario 8: alternative sources of utility data

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
A) AMAGINE-1 all patients						
9: DMF	13.65	£146,101	0.00	£0	-	£16,444
3: Apremilast	13.72	£149,236	0.06	£3,136	Extendedly dominated	£12,307
4: Etanercept	13.81	£151,791	0.15	£5,690	Extendedly dominated	£8,887
2: Adalimumab	14.03	£156,036	0.38	£9,935	Dominated	Dominated
8: Ustekinumab	14.03	£156,156	0.38	£10,055	Dominated	Dominated
7: Secukinumab	14.04	£161,524	0.39	£15,423	Dominated	Dominated
5: Infliximab	14.13	£172,212	0.48	£26,111	Dominated	Dominated
1: Brodalumab	14.23	£155,517	0.57	£9,416	£16,444	N/A
6: Ixekizumab	14.25	£182,957	0.60	£36,857	£1,154,134	£1,154,134
B) York 4th Quartile DLQI						
9: DMF	14.29	£146,101	0.00	£0	-	£16,221
3: Apremilast	14.35	£149,236	0.07	£3,136	Extendedly dominated	£12,208
4: Etanercept	14.45	£151,791	0.16	£5,690	Extendedly dominated	£8,884
2: Adalimumab	14.68	£156,036	0.39	£9,935	Dominated	Dominated
8: Ustekinumab	14.68	£156,156	0.39	£10,055	Dominated	Dominated
7: Secukinumab	14.69	£161,524	0.40	£15,423	Dominated	Dominated
5: Infliximab	14.78	£172,212	0.49	£26,111	Dominated	Dominated
1: Brodalumab	14.87	£155,517	0.58	£9,416	£16,221	N/A
6: Ixekizumab	14.89	£182,957	0.60	£36,857	£1,249,890	£1,249,890

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
C) Secukinumab submission, patients with DLQI > 10						
9: DMF	12.95	£146,101	0.00	£0	-	£30,074
3: Apremilast	12.98	£149,236	0.03	£3,136	Extendedly dominated	£22,362
4: Etanercept	13.03	£151,791	0.08	£5,690	Extendedly dominated	£15,985
2: Adalimumab	13.15	£156,036	0.20	£9,935	Dominated	Dominated
8: Ustekinumab	13.15	£156,156	0.20	£10,055	Dominated	Dominated
7: Secukinumab	13.16	£161,524	0.21	£15,423	Dominated	Dominated
5: Infliximab	13.21	£172,212	0.26	£26,111	Dominated	Dominated
1: Brodalumab	13.26	£155,517	0.31	£9,416	£30,074	N/A
6: Ixekizumab	13.28	£182,957	0.33	£36,857	£1,956,065	£1,956,065
D) Median across all STAs						
9: DMF	12.45	£146,101	0.00	£0	-	£23,277
3: Apremilast	12.49	£149,236	0.04	£3,136	Extendedly dominated	£17,348
4: Etanercept	12.55	£151,791	0.11	£5,690	Extendedly dominated	£12,441
2: Adalimumab	12.71	£156,036	0.26	£9,935	Dominated	Dominated
8: Ustekinumab	12.71	£156,156	0.26	£10,055	Dominated	Dominated
7: Secukinumab	12.72	£161,524	0.27	£15,423	Dominated	Dominated
5: Infliximab	12.79	£172,212	0.34	£26,111	Dominated	Dominated
1: Brodalumab	12.85	£155,517	0.40	£9,416	£23,277	N/A
6: Ixekizumab	12.87	£182,957	0.42	£36,857	£1,567,366	£1,567,366

BRO, brodalumab; BSC, best supportive care; DLQI, Dermatology Life Quality Index; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year; STA, Single Technology Appraisal.

Scenario 9: inclusion of additional adverse events

Following the approached used in the secukinumab and ixekizumab submissions to NICE, the following serious AEs requiring hospitalisation are included in a scenario analysis: NMSC and malignancy other than NMSC and MACE. Serious infections were already included in the base-case analysis. The incidence and costs of these additional adverse events were included in the scenario analysis, but their impact on HRQoL was not.

Anti-TNFs and IL-inhibitors disrupt signalling pathways that are of critical importance to the immune system. In patients with rheumatoid arthritis and inflammatory bowel disease, an increased risk of infection and malignancy has been found in those treated with biologic therapies. However, there is some uncertainty surrounding the risk of adverse events in patients with plaque psoriasis and whether this risk differs for individual drugs and between biologic classes.

Rates of adverse events were obtained from a targeted search of meta-analyses of NMSC, malignancies other than NMSC, and MACE in patients with psoriasis on biologic therapies. Results of the targeted reviews did not provide enough evidence to differentiate between treatments in terms of these adverse events, therefore they were not included in the base-case analysis.

Table 71 Risk of selected adverse events with biologic therapies for psoriasis

Drug class	Point estimate	Range	Source
Non-melanoma skin cancer			
Placebo	0.24%	Not reported	Papp *et al*., 2008 (118)
Anti-TNF	OR 1.33	0.58 to 3.04	Dommasch *et al.,* 2010 (176)
IL-inhibitor	OR 1.33		Assumed same as anti-TNF
Malignancies other than non−melanoma skin cancer			
Placebo	0.25%	Not reported	Dommasch *et al.,* 2010 (176) [b]
Anti-TNF	OR 1.64	OR 0.73 to 3.70	Dommasch *et al.,* 2010 (176)
IL-inhibitor	OR 1.64		Assumed same as anti-TNF
Major adverse cardiovascular events			
Placebo	0.04%	Not reported	Rungapiromnan *et al*., 2016 (177)
Anti-TNF	OR 1.45	OR 0.34 to 6.24	Rungapiromnan *et al*., 2016 (177)
IL-inhibitor	OR 1.45		Assumed same as anti-TNF

[a] Adjusted assuming the reported 0.4% risk is over 20−30 weeks. This is equal to 0.83% (=1−(1−0.004)^(1/25*52)) annually.
[b] Calculated by dividing the number of non-NMSC malignancies in the placebo arm of psoriasis trials by the total n for all placebo arms in psoriasis studies (0.25% = 4/1602).
IL, interleukin; OR, odds ratio; TNF, tumour necrosis factor.

The cost of malignancy other than non−melanoma skin cancer represents the weighted average cost of lymphoma and melanoma. The cost for a MACE was estimated as the weighted average of myocardial infarction and ischaemic stroke. Weights were based on the number of finished consultant episodes described in 2015/16 NHS reference costs for the relevant HRG (142).

Table 72 Unit costs of treatment for adverse events

Adverse event	AE sub-type	Unit cost	Mean cost	Source
NMSC			£2,440	NHS reference costs 2015/16: JC42A (142)
Non−NMSC malignancies	Lymphoma	£5,062	£4,934	NHS reference costs 2015/16: SA31A-F (142)
	Melanoma	£2,440		NHS reference costs 2015/16: JC42A (142)
MACE	Myocardial infarction	£2,177	£3,513	NHS reference costs 2015/16: EB10A-E (142)
	Ischaemic stroke	£4,354		NHS reference costs 2015/16: AA35A-F (142)

AE, adverse event; MACE, major adverse cardiovascular event; NHS, National Health Service; NMSC, non-melanoma skin cancer.

Results of this scenario were similar to the base-case analysis (Table 73).

Table 73 Results of scenario 9: inclusion of additional adverse events

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
9: DMF	12.64	£146,545	0.00	£0	-	£13,383
3: Apremilast	12.72	£149,683	0.07	£3,138	Extendedly dominated	£9,985
4: Etanercept	12.82	£152,241	0.18	£5,696	Extendedly dominated	£7,174
2: Adalimumab	13.10	£156,494	0.46	£9,949	Dominated	Dominated
8: Ustekinumab	13.10	£156,615	0.46	£10,070	Dominated	Dominated
7: Secukinumab	13.11	£161,982	0.47	£15,437	Dominated	Dominated
5: Infliximab	13.23	£172,674	0.59	£26,129	Dominated	Dominated
1: Brodalumab	13.35	£155,982	0.71	£9,437	£13,383	N/A
6: Ixekizumab	13.38	£183,423	0.74	£36,878	£894,033	£894,033

BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year

Scenario 10: alternative efficacy data for ustekinumab

In the base case, efficacy for ustekinumab was based on the NMA outcomes for the weight-based dose of ustekinumab (45 mg for patients weighing ≤ 100 kg, 90 mg for patients weighing > 100 kg) as observed in the relevant RCTs. In this scenario, data for ustekinumab were informed by the evidence from trials that randomised patients to either 45 mg or 90 mg regardless of patient weight. As the mean patient weight in the model was less than 100 kg, the effects for ustekinumab at a 45 mg dose were used.

Results of this scenario were similar to the base-case analysis (Table 74).

Table 74 Results of scenario 10: alternative efficacy data for ustekinumab

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
9: DMF	12.65	£146,163	0.00	£0	-	£13,358
3: Apremilast	12.72	£149,298	0.07	£3,134	Extendedly dominated	£9,955
4: Etanercept	12.83	£151,851	0.18	£5,688	Extendedly dominated	£7,141
2: Adalimumab	13.11	£156,092	0.46	£9,929	Dominated	Dominated
8: Ustekinumab	13.11	£156,212	0.46	£10,049	Dominated	Dominated
7: Secukinumab	13.12	£161,601	0.47	£15,438	Dominated	Dominated
5: Infliximab	13.24	£172,266	0.59	£26,103	Dominated	Dominated
1: Brodalumab	13.35	£155,570	0.70	£9,407	£13,358	N/A
6: Ixekizumab	13.38	£183,011	0.73	£36,848	£894,863	£894,863

BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year

Scenario 11: alternative PASI response criterion

The base-case response threshold for patients to continue treatment in the maintenance phase was PASI 75. In this scenario, PASI 50 was used as an alternative threshold.

The more relaxed criterion for treatment continuation results in slightly higher costs and QALYs for all sequences, and to slightly increased fully incremental ICERs and pairwise ICERs (Table 75).

Table 75 Results of scenario 11: alternative PASI response criterion

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
9: DMF	12.79	£148,860	0.00	£0	-	£16,681
3: Apremilast	12.86	£153,688	0.08	£4,827	Extendedly dominated	£10,706
4: Etanercept	12.97	£157,310	0.19	£8,450	Extendedly dominated	£5,610
2: Adalimumab	13.23	£161,528	0.45	£12,667	Dominated	Dominated
8: Ustekinumab	13.24	£161,690	0.45	£12,829	Dominated	Dominated
7: Secukinumab	13.26	£168,784	0.48	£19,924	Dominated	Dominated
5: Infliximab	13.35	£179,000	0.56	£30,140	Dominated	Dominated
1: Brodalumab	13.45	£159,997	0.67	£11,137	£16,681	N/A
6: Ixekizumab	13.48	£188,862	0.69	£40,002	£1,061,400	£1,061,400

BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year

Scenario 12: alternative values for efficacy of BSC

Response rates were reported according to baseline PASI in Woods *et al.* (2008) (193) and were used as alternative sources for BSC:

A) 0% of patients achieve PASI 50 or higher

B) 65% of patients achieve PASI 50 and 0% achieve PASI 75 or higher

C) 83% of patients achieve PASI 50 and 0% achieve PASI 75 or higher

D) 65% of patients achieve PASI 50 and 30% achieve PASI 75

Increasing the efficacy of BSC beyond the PASI response rates associated with placebo in the NMA results in a reduction in incremental QALYs gained with the most effective therapies, but the ranking of therapies was unchanged (Table 76).

Table 76 Results of scenario 12: alternative values for efficacy of BSC

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
A) 0% of patients achieve PASI 50						
9: Dimethyl Fumarate	12.26	£146,101	0.00	£0.00	-	£12,224
3: Apremilast	12.35	£149,236	0.08	£3,135.52	Extendedly dominated	£9,125
4: Etanercept 50 mg per week	12.47	£151,791	0.20	£5,690.17	Extendedly dominated	£6,547
2: Adalimumab	12.77	£156,036	0.50	£9,934.84	Dominated	Dominated
8: Ustekinumab	12.77	£156,156	0.51	£10,055.34	Dominated	Dominated
7: Secukinumab	12.78	£161,524	0.52	£15,422.84	Dominated	Dominated
5: Infliximab	12.91	£172,212	0.64	£26,110.81	Dominated	Dominated
1: Brodalumab	13.04	£155,517	0.77	£9,415.86	£12,224	N/A
6: Ixekizumab	13.07	£182,957	0.80	£36,856.61	£833,972	£833,972
B) 65% of patients achieve PASI 50 and 0% achieve PASI 75						
9: Dimethyl Fumarate	13.58	£146,101	0.00	£0.00	-	£17,344
3: Apremilast	13.63	£149,236	0.05	£3,135.52	Extendedly dominated	£12,872
4: Etanercept 50 mg per week	13.72	£151,791	0.14	£5,690.17	Extendedly dominated	£9,250
2: Adalimumab	13.92	£156,036	0.35	£9,934.84	Dominated	Dominated
8: Ustekinumab	13.92	£156,156	0.35	£10,055.34	Dominated	Dominated
7: Secukinumab	13.94	£161,524	0.36	£15,422.84	Dominated	Dominated
5: Infliximab	14.03	£172,212	0.45	£26,110.81	Dominated	Dominated
1: Brodalumab	14.12	£155,517	0.54	£9,415.86	£17,344	N/A
6: Ixekizumab	14.15	£182,957	0.57	£36,856.61	£1,089,501	£1,089,501
C) 83% of patients achieve PASI 50 and 0% achieve PASI 75						
9: Dimethyl Fumarate	13.94	£146,101	0.00	£0.00	-	£19,620
3: Apremilast	13.99	£149,236	0.05	£3,135.52	Extendedly dominated	£14,523
4: Etanercept 50 mg per week	14.06	£151,791	0.12	£5,690.17	Extendedly dominated	£10,445
2: Adalimumab	14.24	£156,036	0.30	£9,934.84	Dominated	Dominated
8: Ustekinumab	14.24	£156,156	0.30	£10,055.34	Dominated	Dominated
7: Secukinumab	14.26	£161,524	0.32	£15,422.84	Dominated	Dominated
5: Infliximab	14.34	£172,212	0.40	£26,110.81	Dominated	Dominated
1: Brodalumab	14.42	£155,517	0.48	£9,415.86	£19,620	N/A
6: Ixekizumab	14.44	£182,957	0.50	£36,856.61	£1,190,571	£1,190,571

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
D) 65% of patients achieve PASI 50 and 30% achieve PASI 75						
9: Dimethyl Fumarate	13.95	£146,101	0.00	£0.00	-	£19,694
3: Apremilast	14.00	£149,236	0.05	£3,135.52	Extendedly dominated	£14,576
4: Etanercept 50 mg per week	14.07	£151,791	0.12	£5,690.17	Extendedly dominated	£10,483
2: Adalimumab	14.25	£156,036	0.30	£9,934.84	Dominated	Dominated
8: Ustekinumab	14.25	£156,156	0.30	£10,055.34	Dominated	Dominated
7: Secukinumab	14.27	£161,524	0.31	£15,422.84	Dominated	Dominated
5: Infliximab	14.35	£172,212	0.39	£26,110.81	Dominated	Dominated
1: Brodalumab	14.43	£155,517	0.48	£9,415.86	£19,694	N/A
6: Ixekizumab	14.45	£182,957	0.50	£36,856.61	£1,193,732	£1,193,732

BRO, brodalumab; BSC, best supportive care; DLQI, Dermatology Life Quality Index; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year; STA, Single Technology Appraisal.

Scenario 13: hospitalisation of BSC non-responders

In this scenario, patients with a response to BSC of less than PASI 75 are assumed to require 10.3 inpatient bed days per year, based on the average length of stay for patients with a diagnosis of psoriasis vulgaris who received inpatient care according to 2015/16 NHS Hospital Episode Statistics (191).

Inclusion of hospitalisation costs for BSC non-responders increased the costs for all treatment sequences (Table 77). Brodalumab (sequence 1) was associated with an ICER of £933 per QALY gained versus DMF (sequence 9) and dominated apremilast (sequence 3), etanercept (sequence 4), adalimumab (sequence 2), ustekinumab (sequence 8), infliximab (sequence 5) and secukinumab (sequence 7). The ICER for ixekizumab (sequence 6) versus brodalumab (sequence 1) was £884,326 per QALY.

Table 77 Results of scenario 13: hospitalisation of BSC non-responders

Comparator	Total QALYs	Total costs	Incremental QALYs	Incremental costs	Fully incremental ICER	Pairwise ICER (BRO vs comparator)
9: DMF	12.64	£196,662	0.00	£0	-	£933
3: Apremilast	12.72	£198,755	0.07	£2,093	Dominated	Dominated
4: Etanercept	12.82	£200,002	0.18	£3,339	Dominated	Dominated
2: Adalimumab	13.10	£200,512	0.46	£3,850	Dominated	Dominated
8: Ustekinumab	13.10	£200,633	0.46	£3,970	Dominated	Dominated
7: Secukinumab	13.11	£206,000	0.47	£9,338	Dominated	Dominated
5: Infliximab	13.23	£215,293	0.59	£18,631	Dominated	Dominated
1: Brodalumab	13.35	£197,321	0.71	£658	£933	N/A
6: Ixekizumab	13.38	£224,464	0.74	£27,802	£884,326	£884,326

BRO, brodalumab; BSC, best supportive care; DMF, dimethyl fumarate; ICER, incremental cost-effectiveness ratio, as cost per QALY; N/A, not applicable; QALY, quality-adjusted life-year

B.3.8.4 Summary of sensitivity analyses results

Overall, the sensitivity analysis results show that the economic model is robust across a range of input parameters and assumptions. As in the base-case analysis, in the PSA the cost-effectiveness frontier comprised of brodalumab and ixekizumab. The results of the PSA indicate that brodalumab has a 96% chance of being cost-effective at a willingness-to-pay threshold of £20,000 per QALY.

The deterministic sensitivity analysis explored the impact of varying the efficacy, discontinuation rate and cost of all comparators, as well as BSC. The results show that the costs of the comparators and of BSC have the greatest impact on the model results.

In scenario analyses testing a range of alternative inputs and assumptions, the cost-effectiveness frontier was generally similar to the base-case analysis. The ICER for brodalumab versus DMF, the next non-dominated or extendedly dominated sequence on the cost-effectiveness frontier, was below £20,000 per QALY in the base case and in all but two scenario analyses. Similar results were found for the pairwise comparisons between brodalumab and the comparators. Scenarios in which ICERs above £20,000 per QALY were found were scenario 8C and 8D in which alternative utility values were used.

In the base case and all but one scenario analysis (comparator therapies followed immediately by BSC) brodalumab dominated adalimumab (sequence 2). The brodalumab sequence consistently dominated the sequences starting with ustekinumab (sequence 8), secukinumab (sequence 7) and infliximab (sequence 5) and was consistently more cost-effective than the ixekizumab sequence (sequence 6) at a willingness-to-pay threshold of £30,000 per QALY gained.

B.3.9 Subgroup analysis

It is expected that brodalumab will be used for the treatment of patients with severe psoriasis, defined as a PASI score ≥ 10 and a DLQI > 10. The clinical evidence in the economic model is likely to reflect this patient population: the AMAGINE trials required a minimum PASI score of ≥ 12, while most studies in the NMA used PASI ≥ 10 or ≥ 12 as entry criteria (see section D.1.1.6). There was no DLQI requirement at enrolment in the AMAGINE trials. Accordingly, health state utility estimates used in the base case were based on EQ-5D data from the subgroup of AMAGINE-1 patients with DLQI > 10, consistent with previous NICE TAs.

The results of the subgroup analyses presented in section B.2.7 show that in the AMAGINE trials brodalumab was significantly more efficacious than placebo and ustekinumab regardless of disease severity and prior use of systemic therapy, phototherapy and biological therapy –therefore, no investigation of cost-effectiveness according to subgroups was performed.

B.3.10 Validation of cost-effectiveness analysis

Face validity of the model concept was checked during an advisory board made up of clinical and health economic experts. Following feedback from the advisory board, revisions to the model concept were made and incorporated in its development.

The model underwent quality control to ensure internal and external validity. This was undertaken by the model developers and another health economist who had not been involved in the model's development. Extreme value analysis was used to ensure the model was behaving logically and then a cell-by-cell technical validation of the model was carried out and VBA code checked.

B.3.11 Interpretation and conclusions of economic evidence

Cost-effectiveness models in psoriasis have generally followed the same structure and assumptions as outlined in the 2006 York model (148). The current model framework was based on the York model and modified to address some of the limitations of previous models. The availability of multiple therapeutic options for moderate-to-severe psoriasis have rendered models that do not consider treatment sequences unrealistic. This criticism, raised in ERG reports for previous submissions, has been addressed in the current model, which allows for the comparison of treatment sequences. It also allowed the testing of scenarios incorporating differences in discontinuation rates between therapy classes and variation of assumptions regarding BSC.

Strengths of the economic analysis include the use of QALYs based on directly-elicited utility values as the primary outcome, and the use of PASI 100, representing complete skin clearance, as a distinct response level. Although the 2009 BAD guidelines use PASI 75 as a clinically meaningful endpoint, many patients achieving PASI 75 report that psoriasis still affects their lives (36), and improvements in patient-reported symptom burden and HRQoL have been shown to be greater with PASI 100 than with PASI 75 (35, 36). In addition, the main source of efficacy data is a comprehensive NMA, which was conducted according to NICE Decision Support Unit best practice recommendations (194). The model allowed for variable induction periods in order to align with NICE TAs guidance (70-72, 155-157) and used a 40-year time horizon, a period long enough to capture any differences between sequenced comparators.

Limitations of the analysis include the lack of long-term data for clinical outcomes. The discontinuation rate in the model was based on 3-year data from the UK BADBIR registry (33); however, no suitable data are available to assess discontinuation rates over longer periods. In addition, during maintenance therapy patients are assumed to maintain the same level of PASI response they achieved during induction, until discontinuation. This approach is consistent with all TAs for modelled therapies (70-72, 155-159), and data from the AMAGINE-2 and -3 trials demonstrate stable levels of response up to 52 weeks (responses were maintained during the second year of therapy in the open-label extension phase; see section B.2.6.4). However, longer-term evidence for this assumption is lacking.

There is considerable uncertainty around the efficacy and cost of BSC. The results of the placebo arm in the NMA were used to inform the efficacy of BSC. In the model, BSC comes after hypothetical patients have failed conventional systemic therapies and up to three biologic therapies, so the low efficacy of placebo may be a good representation of the efficacy of BSC for these patients. However, the efficacy of BSC is presumed to be related to its constituents, itself an area of uncertainty. The resource use and associated cost of BSC was sourced from a single UK study performed in 2008 (Fonia *et al.* 2010) (190), although the nature of psoriasis care in the absence of biologic therapies may have changed since then.

The results of this analysis are expected to be applicable to clinical practice in England and Wales, and the base-case analysis used utility values reported by patients in AMAGINE-1 with baseline PASI ≥ 12 and DLQI > 10, consistent with the NICE definition of severe disease (PASI ≥ 10 and DLQI ≥ 10) which is used to identify patients as eligible to receive biological therapy (1).

In conclusion, the cost-effectiveness model shows that brodalumab is likely to be a cost-effective option relative to the comparators in the NICE scope for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy, and for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated.

B.4 References

1. National Institute of Health and Care Excellence. NICE Pathway: Psoriasis. [Updated 5 September 2017. Available from: http://pathways.nice.org.uk/pathways/psoriasis. Accessed: 13 September 2017.]
2. National Institute for Health and Care Excellence. Clinical Guideline 153. Psoriasis: assessment and management. [Updated 4 September 2017. Available from: https://www.nice.org.uk/guidance/cg153/resources/psoriasis-assessment-and-management-35109629621701. Accessed: 4 September 2017.]
3. Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence. Journal of Investigative Dermatology. 2013;133(2):377-85.
4. Springate DA, Parisi R, Kontopantelis E, Reeves D, Griffiths CEM, Ashcroft DM. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. The British Journal of Dermatology. 2017;176(3):650-8.
5. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, 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. Journal of the American Academy of Dermatology. 2008;58(5):826-50.
6. National Psoriasis Foundation. What type of psoriasis do I have? 2017 [Available from: https://www.psoriasis.org/about-psoriasis#type. Accessed: 25 September 2017.]
7. Leino M, Mustonen A, Mattila K, Koulu L, Tuominen R. Influence of Psoriasis on Household Chores and Time Spent on Skin Care at Home: A Questionnaire Study. Dermatology and Therapy. 2015;5(2):107-16.
8. 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. Archives of dermatology. 2001;137(3):280-4.
9. Lynde CW, Poulin Y, Guenther L, Jackson C. The burden of psoriasis in Canada: insights from the pSoriasis Knowledge IN Canada (SKIN) survey. Journal of cutaneous medicine and surgery. 2009;13(5):235-52.
10. Gowda S, Goldblum OM, McCall WV, Feldman SR. Factors affecting sleep quality in patients with psoriasis. Journal of the American Academy of Dermatology. 2010;63(1):114-23.
11. Anstey A, McAteer H, Kamath N, Percival F. Extending psychosocial assessment of patients with psoriasis in the UK, using a self-rateds, web-based survey. Clinical and experimental dermatology. 2012;37(7):735-40.
12. Feldman SR, Zhao Y, Shi L, Tran MH. Economic and Comorbidity Burden Among Patients with Moderate-to-Severe Psoriasis. Journal of managed care & specialty pharmacy. 2015;21(10):874-88.
13. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GB, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol. 2015;135(4):984-91.
14. Mehta NN, Yu Y, Pinnelas R, Krishnamoorthy P, Shin DB, Troxel AB, et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. The American journal of medicine. 2011;124(8):775.e1-6.
15. Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Archives of dermatology. 2007;143(12):1493-9.
16. Lebwohl MG, Bachelez H, Barker J, Girolomoni G, Kavanaugh A, Langley RG, et al. Patient perspectives in the management of psoriasis: Results from the population-based

Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. Journal of the American Academy of Dermatology. 2014;70(5):871-81.e30.
17. Ljosaa TM, Rustoen T, Mork C, Stubhaug A, Miaskowski C, Paul SM, et al. Skin pain and discomfort in psoriasis: an exploratory study of symptom prevalence and characteristics. Acta dermato-venereologica. 2010;90(1):39-45.
18. Armstrong AW, Schupp C, Wu J, Bebo B. Quality of Life and Work Productivity Impairment among Psoriasis Patients: Findings from the National Psoriasis Foundation Survey Data 2003–2011. PLoS ONE. 2012;7(12):e52935.
19. Russo PAJ, Ilchef R, Cooper AJ. Psychiatric morbidity in psoriasis: A review. Australasian Journal of Dermatology. 2004;45(3):155-61.
20. Hrehorow E, Salomon J, Matusiak L, Reich A, Szepietowski JC. Patients with psoriasis feel stigmatized. Acta dermato-venereologica. 2012;92(1):67-72.
21. Weiss SC, Kimball AB, Liewehr DJ, Blauvelt A, Turner ML, Emanuel EJ. Quantifying the harmful effect of psoriasis on health-related quality of life. Journal of the American Academy of Dermatology. 2002;47(4):512-8.
22. Obradors M, Blanch C, Comellas M, Figueras M, Lizan L. Health-related quality of life in patients with psoriasis: a systematic review of the European literature. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2016;25(11):2739-54.
23. Rapp SR, Feldman SR, Exum ML, Fleischer AB, Jr., Reboussin DM. Psoriasis causes as much disability as other major medical diseases. Journal of the American Academy of Dermatology. 1999;41(3 Pt 1):401-7.
24. Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety and suicidality in patients with psoriasis: A population-based cohort study. Archives of dermatology. 2010;146(8):891-5.
25. Lynde CW, Poulin Y, Vender R, Bourcier M, Khalil S. Interleukin 17A: toward a new understanding of psoriasis pathogenesis. Journal of the American Academy of Dermatology. 2014;71(1):141-50.
26. 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. Journal of clinical immunology. 2009;29(2):210-4.
27. Bagel J. Pipeline Focus: IL-17. Practical Dermatology. August 2012:46.
28. Johansen C, Usher PA, Kjellerup RB, Lundsgaard D, Iversen L, Kragballe K. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. Br J Dermatol. 2009;160(2):319-24.
29. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol. 2009;161(5):987-1019.
30. Witte E, Kokolakis G, Witte K, Philipp S, Doecke W-D, Babel N, et al. IL-19 Is a Component of the Pathogenetic IL-23/IL-17 Cascade in Psoriasis. Journal of Investigative Dermatology.134(11):2757-67.
31. Malakouti M, Jacob SE, Anderson NJ. Treatment challenges in the management of moderate-to-severe plaque psoriasis – role of secukinumab. Clinical, Cosmetic and Investigational Dermatology. 2016;9:347-55.
32. Carrascosa JM, van Doorn MB, Lahfa M, Nestle FO, Jullien D, Prinz JC. Clinical relevance of immunogenicity of biologics in psoriasis: implications for treatment strategies. J Eur Acad Dermatol Venereol. 2014;28(11):1424-30.
33. Warren RB, Smith CH, Yiu ZZ, Ashcroft DM, Barker JN, 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(11):2632-40.
34. 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):244-52.

35. Manalo IF, Gilbert KE, Wu JJ. Time to Raise the Bar to Psoriasis Area Severity Index 90 and 100. J Drugs Dermatol. 2015;14(10):1086-8.
36. Strober B, Papp KA, Lebwohl M, Reich K, Paul C, Blauvelt A, et al. Clinical meaningfulness of complete skin clearance in psoriasis. Journal of the American Academy of Dermatology. 2016;75(1):77-82 e7.
37. Papp KA, Reid C, Foley P, Sinclair R, Salinger DH, Williams G, et al. Anti-IL-17 receptor antibody AMG 827 leads to rapid clinical response in subjects with moderate to severe psoriasis: results from a phase I, randomized, placebo-controlled trial. J Invest Dermatol. 2012;132(10):2466-9.
38. Eedy D, Griffiths CEM, Chalmers RJG, Ormerod AD, Smith CH, Barker JNWN, et al. Care of patients with psoriasis: an audit of U.K. services in secondary care. British Journal of Dermatology. 2009;160:557-64.
39. Geale K, Henriksson M, Schmitt-Egenolf M. Evaluating equality in psoriasis healthcare: a cohort study of the impact of age on prescription of biologics. Br J Dermatol. 2016;174(3):579-87.
40. 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.
41. 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.
42. Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis - Protocol. N Engl J Med. 2015;373(14):1318-28.
43. Amgen Inc. A Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-2 (Clinical Study Report). 30 March 2015. Data on file.
44. Amgen Inc. Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-3 (Clinical Study Report). 27 March 2015. Data on file.
45. Amgen Inc. A Phase 3 Study to Evaluate the Efficacy, Safety, and Effect of Withdrawal and Retreatment With Brodalumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-1 (Clinical Study Report). 29 June 2016. Data on file.
46. Paul C, Barker J, Klekotka P, Milmont C, Viswanathan H, Nirula A, et al. Improvements in health-related quality of life measured by SF-36 and EQ-5D in patients with moderate to severe plaque psoriasis treated with brodalumab. Journal of the American Academy of Dermatology. 2016;74(5):AB256.
47. Strober B, Gordon K, Augustin M, Viswanathan H, Klekotka P, Milmont C, et al. Improvements in patient-reported outcomes (PROs) among moderate to severe plaque psoriasis patients treated with brodalumab: Results from AMAGINE-1. Journal of the American Academy of Dermatology. 2016;74(5):AB256.
48. Amgen Inc. A Phase 3 Study to Evaluate the Efficacy, Safety, and Effect of Withdrawal and Retreatment With Brodalumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-1 (Clinical Study Report). 15 May 2015. Data on file.
49. Amgen Inc. A Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-2 (Clinical Study Report). 15 July 2016. Data on file.
50. Amgen Inc. Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-3 (Clinical Study Report). 15 July 2016. Data on file.

51. Nakagawa H, Niiro H, Ootaki K. 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. Journal of dermatological science. 2016;81(1):44-52.
52. Papp KA, Leonardi C, Menter A, Ortonne J-P, Krueger JG, Kricorian G, et al. Brodalumab, an Anti–Interleukin-17–Receptor Antibody for Psoriasis. New England Journal of Medicine. 2012;366(13):1181-9.
53. Amgen Inc. Amgen to Terminate Participation in Co-development and Commercialization of Brodalumab. [Updated 22 May 2015. Available from: http://wwwext.amgen.com/media/news-releases/2015/05/amgen-to-terminate-participation-in-co-development-and-commercialization-of-brodalumab/. Accessed: 21 December 2016.]
54. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report: Kyntheum (brodalumab). 2017 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003959/WC500232916.pdf. Accessed: 16 August 2017.]
55. SmPC: brodalumab 210 mg for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy. [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003959/WC500232913.pdf. Accessed: 25 September 2017.]
56. 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. British Journal of Dermatology. 2017:n/a-n/a.
57. Feldman S, Krueger G. Psoriasis assessment tools in clinical trials. Annals of the Rheumatic Diseases. 2005;64(Suppl 2):ii65-ii8.
58. Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. Journal of the American Academy of Dermatology. 2003;49(2):206-12.
59. Thaci D, Daiber W, Boehncke WH, Kaufmann R. Calcipotriol solution for the treatment of scalp psoriasis: evaluation of efficacy, safety and acceptance in 3,396 patients. Dermatology. 2001;203(2):153-6.
60. Bushnell DM, Martin ML, McCarrier K, Gordon K, Chiou C-F, Huang X, et al. Validation of the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure to assess psoriasis symptom severity. Journal of Dermatological Treatment. 2013;24(5):356-60.
61. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clinical and experimental dermatology. 1994;19(3):210-6.
62. Shikiar R, Harding G, Leahy M, Lennox RD. Minimal Important Difference (MID) of the Dermatology Life Quality Index (DLQI): Results from patients with chronic idiopathic urticaria. Health and Quality of Life Outcomes. 2005;3:36-.
63. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol. 2005;125(4):659-64.
64. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica Scandinavica. 1983;67(6):361-70.
65. Papp KA, Fonjallaz P, Casset-Semanaz F, Krueger JG, Wittkowski KM. Approaches to reporting long-term data. Current medical research and opinion. 2008;24(7):2001-8.
66. 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(2):510-8.
67. Valeant presentation to Food and Drugs Administration. Brodalumab - Dermatologic and Ophthalmic Drugs Advisory Committee. 2016 [Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM513235.pdf. Accessed: 25 May 2017.]

68. Papp K, Reich K, Paul C, Blauvelt A, Toth D, Langley RG, et al. Improvements in depression and anxiety with brodalumab therapy in AMAGINE-1, a phase 3 study for moderate to severe plaque psoriasis. Journal of the American Academy of Dermatology. 2016;74(5):AB254.
69. Shikiar R, Willian M, Okun M, Thompson C, Revicki D. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. Health and Quality of life outcomes. 2006;4(71).
70. National Institute for Health and Care Excellence. Ustekinumab for the treatment of adults with moderate to severe psoriasis TA180. London: National Institute for Health and Care Excellence; 2009.
71. National Institute for Health and Care Excellence. Single Technology Appraisal: Secukinumab for the treatment of moderate to severe plaque psoriasis [TA350] Committee Papers. London, UK: National Institute for Health and Care Excellence. 2015 [cited 2017 31 Jan]. Available from: https://www.nice.org.uk/guidance/TA350/documents/secukinumab-for-treating-moderate-to-severe-plaque-psoriasis-committee-papers2. Accessed: 31 January.]
72. National Institute for Health and Care Excellence. Single Technology Appraisal: Ixekizumab for treating moderate to severe plaque psoriasis [ID904] Committee Papers. [Internet]. London, UK: National Institute for Health and Care Excellence. 2016 [cited 2017 Jan 31]. Available from: https://www.nice.org.uk/guidance/GID-TA10063/documents/committee-papers-3. Accessed: 31 January.]
73. 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(5):1109-17.
74. 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. 2016.
75. Thaci D, Blauvelt A, Reich K, Tsai TF, 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. Journal of the American Academy of Dermatology. 2015;73(3):400-9.
76. 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.
77. 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(8):837-46.
78. 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. Journal of the American Academy of Dermatology. 2008;58(1):106-15.
79. 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. The Journal of dermatology. 2010;37(4):299-310.
80. 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(4):598-606.
81. Bissonnette R, Tardif JC, Harel F, Pressacco J, Bolduc C, Guertin MC. 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. Circulation Cardiovascular imaging. 2013;6(1):83-90.

82. Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK, 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):405-17.
83. 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.
84. 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. Lancet (London, England). 2012;380(9843):738-46.
85. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, 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.
86. 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.
87. 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. J Eur Acad Dermatol Venereol. 2013;27(3):e376-83.
88. 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. The Journal of dermatology. 2017;44(8):873-84.
89. Reich K, Soung J, Gooderham M, Zhang Z, Nograles K, Goodfield M. Sustained efficacy of apremilast in patients with moderate to severe psoriasis who continued on apremilast or switched from etanercept treatment: 52-week results from the LIBERATE study. Journal of the American Academy of Dermatology. 2016;1):AB276.
90. 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.
91. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Archives of dermatology. 2003;139(12):1627-32; discussion 32.
92. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, 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):1304-12.
93. Van de Kerkhof PCM, S. Segaert, M. Lahfa, T.A. Luger, Z. Karolyi,§ A. Kaszuba, G. Leigheb, F.M. Camacho, D. Forsea, C. Zang, M.P. Boussuge, L. Paolozzi and J. Wajdula. 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):1177-85.
94. 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. Journal of the American Academy of Dermatology. 2012;67(1):86-92.
95. Bachelez H, van de Kerkhof PC, Strohal R, Kubanov A, Valenzuela F, Lee JH, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. Lancet (London, England). 2015;386(9993):552-61.

96. 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 (London, England). 2006;367(9504):29-35.
97. 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). The Journal of dermatological treatment. 2013;24(3):169-78.
98. Gottlieb AB, C. Leonardi, F. Kerdel, S. Mehlis, M. Olds and D.A. Williams. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. British Journal of Dermatology. 2011;165:652-60.
99. 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(3):661-8.
100. 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 (London, England). 2017;390(10091):276-88.
101. de Vries AC, Thio HB, de Kort WJ, Opmeer BC, van der Stok HM, de Jong EM, et al. A prospective randomised controlled trial comparing infliximab and etanercept in patients with moderate to severe chronic plaque type psoriasis Psoriasis Infliximab versus Etanercept Comparison Evaluation, the PIECE study. Br J Dermatol. 2016.
102. Yang HZ, Wang K, Jin HZ, Gao TW, Xiao SX, Xu JH, et al. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. Chinese medical journal. 2012;125(11):1845-51.
103. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet (London, England). 2005;366(9494):1367-74.
104. 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 (London, England). 2001;357(9271):1842-7.
105. Gottlieb AB, MD, PhD, Evans, Robert, PharmD., Li, Shu MS., Dooley, Lisa T. DrPH., Guzzo, Cynthia A. MD., Baker, Daniel MD., Bala, Mohan PhD., Marano, Colleen W. PhD., Menter, Alan MD. Infliximab induction therapy for patients with severe plaque-type psoriasis: A randomized, double-blind, placebo-controlled trial. Journal American Academy of Dermatology. 2004;51(4):534-42.
106. 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. Journal of the American Academy of Dermatology. 2007;56(1):31 e1-15.
107. Torii H, Nakagawa H, Japanese Infliximab Study i. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. Journal of dermatological science. 2010;59(1):40-9.
108. 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.
109. Griffiths CE, 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 (London, England). 2015;386(9993):541-51.
110. 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.

111. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. 2014;371(4):326-38.
112. Novartis Pharmaceuticals. Efficacy and Safety of Subcutaneous Secukinumab for Moderate to Severe Chronic Plaque-type Psoriasis for up to 1 Year (ERASURE). In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000 [cited 2017 Jan 31]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT01365455?sect=Xd0156. Accessed: 31 January.]
113. Paul C, Lacour, J.P., Tedremets, L., Kreutzer, K., Jazayeri, S., Adams, S., Guindon, C., You, R., Papavassilis, C. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). Journal of European Academy of Dermatology and Venereology. 2015:1082-90.
114. 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). Journal of the American Academy of Dermatology. 2015;73(1):27-36 e1.
115. Novartis Pharmaceuticals. Efficacy and Safety of Subcutaneous Secukinumab (AIN457) for Moderate to Severe Chronic Plaque-type Psoriasis Assessing Different Doses and Dose Regimens (SCULPTURE). In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000 [cited 2017 Jan 31]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT01406938?term=SCULPTURE&rank=1. Accessed: 31 January.]
116. Tsai TF, Ho JC, Song M, Szapary P, Guzzo C, Shen YK, 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). Journal of dermatological science. 2011;63(3):154-63.
117. 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 (London, England). 2008;371(9625):1665-74.
118. 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 (London, England). 2008;371(9625):1675-84.
119. 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.
120. Griffiths CE, 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.
121. Igarashi A, Kato T, Kato M, Song M, Nakagawa H, Japanese Ustekinumab Study G. 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. The Journal of dermatology. 2012;39(3):242-52.
122. 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(R) - and placebo-controlled trial (BRIDGE). Br J Dermatol. 2017;176(3):615-23.
123. 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(6):1345-9.

124. Sharp SJ, Thompson SG. Analysing the relationship between treatment effect and underlying risk in meta-analysis: comparison and development of approaches. Stat Med. 2000;19(23):3251-74.
125. Sharp SJ, Thompson SG, Altman DG. The relation between treatment benefit and underlying risk in meta-analysis. BMJ. 1996;313(7059):735-8.
126. Thompson SG, Smith TC, Sharp SJ. Investigating underlying risk as a source of heterogeneity in meta-analysis. Stat Med. 1997;16(23):2741-58.
127. Papp K, Leonardi C, Menter A, Thompson EH, Milmont CE, Kricorian G, et al. Safety and efficacy of brodalumab for psoriasis after 120 weeks of treatment. Journal of the American Academy of Dermatology. 2014;71(6):1183-90.e3.
128. Amgen Inc. A Long-term Assessment of the Safety and Efficacy of AMG 827 Subcutaneous Treatment in Subjects With Psoriasis. (Clinical Study Report). Data on file.
129. Valeant Food and Drugs Administration sponsor briefing document. Brodalumab injection - Dermatologic and Ophthalmic Drugs Advisory Committee. 2016 [Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM511360.pdf. Accessed: 30 May 2017.]
130. Conti HR, Gaffen SL. IL-17-mediated immunity to the opportunistic fungal pathogen Candida albicans. Journal of immunology (Baltimore, Md : 1950). 2015;195(3):780-8.
131. FDA. Clinical Outcome Assessment Review - Ixekizumab. 2016 [Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125521Orig1s000MedR.pdf. Accessed: 16 December 2016.]
132. FDA. Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. 2012 [Available from: http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm315156.htm. Accessed: 16 December 2016.]
133. Valeant Food and Drugs Administration sponsor briefing document - errata. Brodalumab injection - Dermatologic and Ophthalmic Drugs Advisory Committee. 2016 [Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM511361.pdf. Accessed: 30 May 2017.]
134. FDA. FDA Briefing Document Dermatologic and Ophthalmic Drugs Advisory Committee Meeting July 19 2016: Background Package for BLA 761032 Siliq (brodalumab) injection, 210 mg/1.5 ml. 2016 [Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM511357.pdf. Accessed: 19 August 2017.]
135. Chiricozzi A, Romanelli M, Saraceno R, Torres T. No meaningful association between suicidal behavior and the use of IL-17A-neutralizing or IL-17RA-blocking agents. Expert Opinion on Drug Safety. 2016;15(12):1653-9.
136. Wozel G. Psoriasis treatment in difficult locations: scalp, nails, and intertriginous areas. Clinics in dermatology. 2008;26(5):448-59.
137. Reich K. Approach to managing patients with nail psoriasis. J Eur Acad Dermatol Venereol. 2009;23 Suppl 1:15-21.
138. de Jong EM, Seegers BA, Gulinck MK, Boezeman JB, van de Kerkhof PC. Psoriasis of the nails associated with disability in a large number of patients: results of a recent interview with 1,728 patients. Dermatology. 1996;193(4):300-3.
139. Khobzey K, Liskova I, Szegedi A, Pavlovsky L, Lunder T, Kingo K, et al. Effectiveness of adalimumab in the treatment of scalp and nail affection in patients with moderate to severe plaque psoriasis in routine clinical practice. Acta dermatovenerologica Alpina, Pannonica, et Adriatica. 2017;26(1):11-4.
140. Torbica A, Fattore G, Ayala F. Eliciting preferences to inform patient-centred policies: the case of psoriasis. PharmacoEconomics. 2014;32(2):209-23.

141. Brezinski EA, Armstrong AW. Off-Label Biologic Regimens in Psoriasis: A Systematic Review of Efficacy and Safety of Dose Escalation, Reduction, and Interrupted Biologic Therapy. PLoS ONE. 2012;7(4):e33486.
142. Department of Health. NHS Reference Costs. 2015–16 [
143. Langley RG, Lebwohl M, Krueger GG, Szapary PO, Wasfi Y, Chan D, et al. Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up. Br J Dermatol. 2015;172(5):1371-83.
144. Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Cause-specific mortality in patients with severe psoriasis: A population-based cohort study in the United Kingdom. The British journal of dermatology. 2010;163(3):586-92.
145. National Institute for Health and Care Excellence. Resource impact report: Ixekizumab for treating moderate to severe plaque psoriasis (TA442). 2017 [Available from: https://www.nice.org.uk/guidance/ta442/resources/resource-impact-report-pdf-4429529677. Accessed: 23 August 2017.]
146. Office of National Statistics. Dataset: Subnational Population Projections for Regions in England: Table 1. 2016.
147. Hendrix N, Ollendorf D, Chapman RH, Loos A, Liu S, Kumar V, et al. Cost-effectiveness of targeted therapy for moderate-to-severe plaque psoriasis: An analysis based on an institute for clinical and economic review (ICER) report. Value in Health. 2017;20 (5):A158.
148. Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, et al. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technology Assessment. 2006;10(iii–iv, xiii–xvi):1–239.
149. Lloyd A, Reeves P, Conway P, Reynolds A, Baxter G. Economic evaluation of etanercept in the management of chronic plaque psoriasis. British Journal of Dermatology. 2009;160(2):380-6.
150. Sizto S, Bansback N, Feldman S, Willian M, Anis A. Economic evaluation of systemic therapies for moderate to severe psoriasis. British Journal of Dermatology. 2009;160(6):1264-72.
151. Johansson E, Svedbom A, Kumar G, Hartz S, Kiri S. Cost-effectiveness analysis of ixekizumab vs. Secukinumab in sequential biologic treatment of psoriasis in the UK. Value in Health. 2016;19 (7):A568.
152. Mughal F, Cawston H, Kinahan D, Morris J, Tencer T, Zhang F. Cost-effectiveness of apremilast in moderate to severe psoriasis in Scotland. Value in Health. 2015;18 (7):A420.
153. Mughal F, Barker J, Cawston H, Damera V, Bewley A, Morris J, et al. Cost-effectiveness of apremilast in moderate to severe psoriasis in the UK. Journal of the American Academy of Dermatology. 2016;1):AB243.
154. Sawyer LM, Wonderling D, Jackson K, Murphy R, Samarasekera EJ, Smith CH. Biological Therapies for the Treatment of Severe Psoriasis in Patients with Previous Exposure to Biological Therapy: A Cost-Effectiveness Analysis. PharmacoEconomics. 2015;33(2):163-77.
155. National Institute for Health and Care Excellence. Etanercept and efalizumab for the treatment of adults with psoriasis TA103. 2006.
156. National Institute for Health and Care Excellence. Infliximab for the treatment of adults with psoriasis TA134. London; 2008.
157. National Institute for Health and Care Excellence. Adalimumab for the treatment of adults with psoriasis TA146. London; 2008.
158. National Institute for Health and Care Excellence. Single Technology Appraisal: Apremilast for treating moderate to severe plaque psoriasis [TA419] Committee Papers. London, UK: National Institute for Health and Care Excellence. 2016 [Available from: https://www.nice.org.uk/guidance/ta419/documents/committee-papers-2. Accessed: 5 September 2017.]

159. National Institute for Health and Care Excellence. Technology Appraisal Guidance: Dimethyl fumarate for treating moderate to severe plaque psoriasis [TA475] London, UK: National Institute for Health and Care Excellence. 2017 [Available from: https://www.nice.org.uk/guidance/ta475/resources/dimethyl-fumarate-for-treating-moderate-to-severe-plaque-psoriasis-pdf-82604967702469. Accessed: 6 September.]
160. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013 London: National Institute for Health and Care Excellence. 2013 [Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Accessed: 8 March 2017.]
161. New Therapies Subgroup (Greater Manchester Medicines Management Group). The sequential use of biologic agents in the treatment of chronic or plaque psoriasis for those patients fulfilling NICE criteria for a biologic 2015. [Available from: http://gmmmg.nhs.uk/docs/nts/NTS%20Biologic%20Agents%20-%20Sequential%20use%20in%20Psoriasis%200715.pdf. Accessed: 5 September 2017.]
162. Inzinger M, Wippel-Slupetzky K, Weger W, Richter L, Mlynek A, Fleischander B, 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):207-12.
163. 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. Br J Dermatol. 2014;171(4):875-83.
164. van den Reek JM, Zweegers J, Kievit W, Otero ME, van Lumig PP, Driessen RJ, et al. 'Happy' drug survival of adalimumab, etanercept and ustekinumab in psoriasis in daily practice care: results from the BioCAPTURE network. Br J Dermatol. 2014;171(5):1189-96.
165. Leonardi C, Papp K, Strober B, Reich K, Asahina A, Gu Y, et al. The long-term safety of adalimumab treatment in moderate to severe psoriasis: a comprehensive analysis of all adalimumab exposure in all clinical trials. American journal of clinical dermatology. 2011;12(5):321-37.
166. Papp KA, Griffiths CE, Gordon KB, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br J Dermatol. 2013;48(11):844-54.
167. Pariser DM, Leonardi CL, Gordon K, Gottlieb AB, Tyring S, Papp KA, et al. Integrated safety analysis: short- and long-term safety profiles of etanercept in patients with psoriasis. Journal of the American Academy of Dermatology. 2012;67(2):245-56.
168. Reich K, Wozel G, Zheng H, van Hoogstraten HJ, Flint L, Barker J. Efficacy and safety of infliximab as continuous or intermittent therapy in patients with moderate-to-severe plaque psoriasis: results of a randomized, long-term extension trial (RESTORE2). Br J Dermatol. 2013;168(6):1325-34.
169. Yiu ZZN, Exton LS, Jabbar-Lopez Z, Mohd Mustapa MF, Samarasekera EJ, Burden AD, et al. Risk of Serious Infections in Patients with Psoriasis on Biologic Therapies: A Systematic Review and Meta-Analysis. Journal of Investigative Dermatology. 2016;136(8):1584-91.
170. Rustin MHA. Long-term safety of biologics in the treatment of moderate-to-severe plaque psoriasis: review of current data. British Journal of Dermatology. 2012;167:3-11.
171. Tan X, Balkrishnan R, Feldman SR. Infections associated with the use of tumor necrosis factor-alpha inhibitors in psoriasis. J Drugs Dermatol. 2013;12(3):e41-5.
172. Garcia-Doval I, Carretero G, Vanaclocha F, et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: Patients ineligible vs eligible for randomized controlled trials. Archives of dermatology. 2012;148(4):463-70.
173. Kalb RE, Fiorentino DF, Lebwohl MG, et al. Risk of serious infection with biologic and systemic treatment of psoriasis: Results from the psoriasis longitudinal assessment and registry (psolar). JAMA dermatology. 2015;151(9):961-9.

174. 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.
175. Blauvelt A, Reich K, Tsai TF, Tyring S, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. Journal of the American Academy of Dermatology. 2017;76(1):60-9 e9.
176. Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand JM. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. J Am Acad Dermatol 2011 64(6):1035-50.
177. Rungapiromnan W, Yiu ZZN, Warren RB, Griffiths CEM, Ashcroft DM. Impact of Biologic Therapies on Risk of Major Adverse Cardiovascular Events in Patients with Psoriasis: Systematic Review and Meta-analysis of Randomised Controlled Trials. British Journal of Dermatology. 2016.
178. Peleva E, Exton LS, Kelley K, Mason KJ, Smith CH. Risk of Cancer in Patients with Psoriasis on Biologic Therapies: A Systematic Review. British Journal of Dermatology.n/a-n/a.
179. Office for National Statistics. Life Expectancy at Birth and at Age 65 for the UK and Local Areas in England and Wales. 2015 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/interimlifetablesenglandandwales. Accessed: 5 September 2017.]
180. Knight C, Mauskopf J, Ekelund M, Singh A, Yang S, Boggs R. Cost-effectiveness of treatment with etanercept for psoriasis in Sweden. European Journal of Health Economics. 2012(13):145-56.
181. Sherif B, Graham CN, Neidhardt K, Gilloteau I, O'Neill CB, McBride D, 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.
182. Anis A, Bansback N, Szito S, Gupta S, Willian M, Feldman S. Economic evaluation of biologic therapies for the treatment of moderate to severe psoriasis in the United States. Journal of Dermatological Treatment.22(2):65-74.
183. Pickard AS, Gooderham M, Hartz S, Nicolay C. EQ-5D health utilities: exploring ways to improve upon responsiveness in psoriasis. Journal of Medical Economics. 2017;20(1):19-27.
184. Pan F, Brazier N, Shear NH, Jivraj F, Schenkel B, Brown R. Cost Utility Analysis Based on a Head-to-Head Phase 3 Trial Comparing Ustekinumab and Etanercept in Patients with Moderate-to-Severe Plaque Psoriasis: A Canadian Perspective. Value in Health. 2011;14:652-6.
185. Revicki D, Willian MK, Saurat JH, Papp KA, Ortonne JP, Sexton C, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. The British journal of dermatology. 2008;158(3):549-57.
186. Diamantopoulos A, Finckh A, Huizinga T, Sungher DK, Sawyer L, Neto D, et al. Tocilizumab in the Treatment of Rheumatoid Arthritis: A Cost-Effectiveness Analysis in the UK. PharmacoEconomics. 2014;32(8):775-87.
187. Sisk JE, Moskowitz AJ, Whang W, Lin JD, Fedson DS, McBean AM, et al. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. Jama. 1997;278(16):1333-9.
188. Monthly Index of Medical Specialties, August 2017 [Internet].
189. Curtis L, Burns A. Unit Costs of Health & Social Care 2016 Canterbury, Kent: Personal Social Services Research Unit 2016 [Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php. Accessed: 5 September 2017.]

190. Fonia A, Jackson K, LeReun C, D.M. Grant, Barker JNWN, 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. British Journal of Dermatology. 2010;163 (4):807–16.
191. National Health Service. Hospital Episode Statistics, 2015–16. 2016 [Available from: http://content.digital.nhs.uk/hes.
192. NHS Reference Costs [Internet]. 2014-15.
193. Woods AL, Rutter KJ, Gardner LS, Lewis VJ, Saxena S, George SA, et al. Inpatient management of psoriasis: a multicentre service review to establish national admission standards. British association of dermatologists 2007;158:266-72.
194. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making. 2013;33(5):607-17.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Brodalumab for treating moderate to severe plaque psoriasis in adults [ID878]

Dear Company,

The Evidence Review Group, CRD and CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York, and the technical team at NICE have looked at the submission received on 27 September from LEO Pharma. 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 **30 October**. 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 Lucy Beggs, Technical Lead (lucy.beggs@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Section A: Clarification on effectiveness data

Additional information required

A1. The reference list includes 242 references (for the main submission and the appendices) but only 186 references were provided. Please send copies of the references referred to in the appendices.

A2. **Priority Question:** Page 90 describes a review of published data on other psoriasis agents to compare suicidal ideation and behaviour event rates with brodalumab. Please provide further details and results of this review.

A3. Please provide further information on the advisory board meetings (e.g. for estimating discontinuation, referred to on page 120), such as meeting minutes and names of clinicians involved.

Systematic review

A4. **Priority Question:** It is unclear whether eligibility criteria stated in the appendices are for the Systematic Literature Review (SLR) or Network Meta-analysis (NMA). Please clarify whether the eligibility criteria presented in tables 78 and 79 are for the NMA (including trials of the different systemic therapies) or for the review of brodalumab studies included in the submission (Document B). Should the title of table 78 be 'Eligibility criteria for biologics and apremilast NMA study selection' and table 79 'Eligibility criteria for DMF NMA study selection'? If these are criteria for the NMA, please present details of the eligibility criteria for the SLR.

A5. **Priority Question:** The ERG have identified a placebo-controlled RCT of brodalumab (Papp et al., NEJM 2012) that was not included in the SLR/submission (although it was included in the NMA). Please explain why this trial was not described in the submission. Please confirm that there are no other relevant RCTs.

A6. Table 80 (Appendix) presents a list of studies excluded from the NMA with reasons for exclusion. Is a similar table available for studies excluded from the SLR with reasons for exclusion?

A7. Table 80 states a reason for exclusion from NMA as 'secondary publication reporting outcomes other than PASI', however, several non-PASI outcomes were listed as inclusion criteria in tables 78 and 79. Please justify the exclusion of non-PASI outcomes.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

AMAGINE trials

A8. Please confirm how many patients in each treatment arm in the AMAGINE trials were from the UK.

A9. **Priority Question:** On page 41 of the company submission, it states that *'For 12-week analyses of PASI, sPGA, PSI and PSSI (AMAGINE-1 only) response rates, missing data were imputed by non-responder imputation (NRI) for dichotomous endpoints (40, 41) […] For analyses of all other patients during the maintenance phase, missing values for dichotomous endpoints were imputed by NRI, unless otherwise specified; continuous variables were imputed using LOCF.'* Please provide additional details; for example, how many values were imputed for:

a. each treatment group

b. each outcome

c. each timepoint?

A10. The EMA report refers to a subgroup analysis based on weight (≤100kg vs. >100kg.). Please provide results for this analysis. Are there any additional subgroup analyses that were performed, but not reported in the submission?

A11. **Priority Question:** Tables 121-123 (Appendix) report reasons that patients discontinued from the AMAGINE studies. Please provide further information about the categories 'full consent withdrawn' and 'other', because these make up the majority of patients who discontinued.

A12. **Priority Question:** Please add data on the number of patients included in analyses at each timepoint for Figures 6-11, 13-15, 19-20 and 24.

A13. Table 16 presents the proportion of patients receiving rescue therapy in AMAGINE-2 and AMAGINE-3. Patients in the ustekinumab group could receive rescue therapy with brodalumab or ustekinumab; please clarify whether patients were randomly assigned to these rescue therapies?

A14. Table 24 includes patients treated with other doses of brodalumab or with ustekinumab, in the maintenance phase before changing to brodalumab 210 mg every 2 weeks in the open-label extension phase. Please provide subgroup data for patients who received brodalumab 210 mg every 2 weeks during the maintenance phase (i.e. excluding patients who received lower doses of brodalumab or who received ustekinumab during the maintenance phase).

A15. Please provide further information on the [redacted] deaths that occurred during the open-label extension of AMAGINE-2 and AMAGINE-3, (page 84). Page 84 directs readers

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

to section B.2.10.3.1, which refers to Appendix F Tables 102-104. However, Tables 102-104 only report [redacted] fatal adverse events.

Network Meta-Analysis

A16. Please give further details of why Krueger (2007) (a human interleukin-12/23 monoclonal antibody for the treatment of psoriasis NCT00320216) was excluded from the network meta-analysis.

A17. Please provide pairwise comparisons of the relative risk (with 95% credible interval) of achieving a PASI ≥75 response for all interventions in the base case NMA.

A18. **Priority Question:** Please provide additional results from NMA sensitivity analysis 1 (section B.2.9.3.2), which only includes EMA licensed doses that are currently recommended by NICE:

a. Please provide the absolute predicted PASI 75, 90 and 100 responses (with 95% credible interval) for all interventions, i.e., the equivalent of Table 26 for sensitivity analysis 1.

b. Please provide pairwise comparisons of the relative risk (with 95% credible interval) of achieving a PASI ≥75 response for all interventions from sensitivity analysis 1.

c. Please provide the results of sensitivity analysis 1 in the form of Convergence Diagnostic and Output Analysis (CODA) for use in the economic model.

A19. **Priority Question:** Please provide additional results from NMA sensitivity analysis 4 (section B.2.9.3.2), which excluded studies reporting greater than 30% of randomised patients having previously tried biological therapy:

a. Please provide the absolute predicted PASI 75, 90 and 100 responses (with 95% credible interval) for all interventions, i.e., the equivalent of Table 26 for sensitivity analysis 4.

b. Please provide pairwise comparisons of the relative risk (with 95% credible interval) of achieving a PASI ≥75 response for all interventions from sensitivity analysis 4.

c. Please provide the results of sensitivity analysis 4 in the form of CODA for use in the economic model.

d. Please provide clinical evidence to show the importance of the 30% threshold used in sensitivity analysis 4 for randomised patients who had previously tried biological therapy.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

e. Please clarify whether or not trials that did not report a % of patients having previously tried biological therapy were included in the NMA of sensitivity analysis 4.

A20. **Priority Question:** Please provide the predicted PASI 75, 90 and 100 responses for all interventions and the associated CODA for use in the economic model for:

a. The NMA that excludes all phase II studies.

b. The NMA that excludes the two brodalumab phase II trials, i.e., excluding Nakagawa et al., (2016) and Papp et al., (2012).

A21. **Priority Question:** Please provide additional results from the placebo adjusted model:

a. Please provide the absolute predicted PASI 75, 90 and 100 responses (with 95% credible interval) for all interventions, i.e., the equivalent of Table 26 for the placebo adjusted model.

b. Please provide the relative risk at each PASI response (with 95% credible interval) for all interventions versus placebo, i.e., the equivalent of Table 27 for the placebo adjusted model.

c. Please provide the relative risk at each PASI response (with 95% credible interval) for brodalumab 210 mg versus comparator interventions, i.e., the equivalent of Table 28 for the placebo adjusted model.

d. Please provide pairwise comparisons of the relative risk (with 95% credible interval) of achieving a PASI ≥75 response for all interventions.

e. Please provide the programming WinBUGS code for the placebo adjusted model.

A22. The WinBUGS code uses [redacted] for the baseline placebo effect. Please provide an explanation for how these quantities were estimated. Please provide details of any evidence used to support this estimation.

Section B: Clarification on cost-effectiveness data

Health-related quality of life

B1. **Priority Question:** Please provide justification for using a complete case analysis approach for EQ-5D data from the AMAGINE-1 trial.

a. Please tabulate the volume of missing EQ-5D data at each time point from baseline to week 12.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

b. Please explain why imputation methods were not used for missing EQ-5D data.

B2. **Priority Question:** Please provide details of the regression methods used on the individual patient data and the associated measures of goodness of fit in order to estimate change in EQ-5D from baseline to 12 weeks.

a. Please clarify whether correlation between utility values for one individual at different assessment points was taken into account, and whether a repeated measures model was used.

b. Please provide details on how the EQ-5D-5L was converted to the EQ-5D-3L.

c. Please provide justification for why the regression model adjusted for baseline DLQI and not baseline EQ-5D.

B3. **Priority Question:** In order to assess alternative specifications of the EQ-5D regression model, please provide additional utility estimates (with uncertainty) and associated measures of goodness of fit for the following specifications:

a. EQ-5D regression model adjusted for baseline EQ-5D score.

b. EQ-5D regression model adjusted for baseline EQ-5D score and baseline PASI, with and without adjustment for baseline DLQI.

c. The above specifications (a. and b.) for the subgroup with a baseline DLQI > 10.

B4. **Priority Question:** To assess the generalisability of the EQ-5D data reported in the AMAGINE-1 trial to the AMAGINE-2 and AMAGINE-3 trials, please provide additional comparisons across these trials for mapping between DLQI and EQ-5D. Please present EQ-5D estimates for each PASI outcome separately for each trial (AMAGINE-1, 2 and 3) using a published and validated mapping function.

Best Supportive Care (BSC)

B5. **Priority Question:** Please provide a break-down of the resource use and unit cost values used to estimate annual costs of (i) medication and (ii) inpatient admissions and outpatient care associated with BSC.

a. Please tabulate each element of resource use derived from Fonia et al., (2010) separately and include:

i. The unit cost applied to these elements.

ii. Before and after inflation indexing and provide details of index used.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

iii. Pre- and post-biologics.

b. Please state all assumptions that were used to estimate the costs of BSC.

Effect modification

B6. Please provide details on how scenario 4A (page 146) was implemented in the model.

a. Please clarify whether the adjustment was applied to all lines of therapy or only second and third lines

b. Please clarify whether the adjustment was applied to all treatments or only biological therapy.

Section C: Textual clarifications and additional points

C1. Please clarify whether the pack cost for Apremilast reported in Table 50 should read £265.18 rather than £256.18.

C2. The numbers in n Figure 33 (PRISMA diagram) do not appear to add up. In the 'original biologics and apremilast SLR' flow diagram, 225 full text papers were assessed for eligibility with an additional 31 records identified by supplementary searching; 150 records did not meet inclusion criteria, therefore, 106 records should have been included in the SLR, rather than 98. Please explain the discrepancy. In the 'update biologics and apremilast SLR', 17 RCTs were included in the SLR. Twelvedid not meet inclusion criteria of NMA, which should have left 5 RCTs included in the NMA, rather than 6, as reported in the flow chart. Again, please explain the discrepancy.

C3. Please explain why figures in Section D.1.2 (Figure 34 to Figure 36) do not always add up (e.g. received IP n=297, completed phase n=274, entered rescue n=0, discontinued phase n=22) and send corrected figures, if appropriate.

Single technology appraisal

Brodalumab for treating moderate to severe plaque psoriasis in adults [ID878]

Section A: Clarification on effectiveness data

Additional information required

A1. The reference list includes 242 references (for the main submission and the appendices) but only 186 references were provided. Please send copies of the references referred to in the appendices.

We apologise for the omission. The references for the Appendices have now been uploaded to NICEDocs. There are 3 references (1 in the main submission and 2 in the appendices) that could not be provided as they are either a website or book:

188. Monthly Index of Medical Specialties, August 2017 [Internet].
201. British Medical Association. British national formulary, No. 48. London. 2004.
205. HODaR Database 2004. Available from: http://www.hodar.co.uk/.

A2. Priority Question: Page 90 describes a review of published data on other psoriasis agents to compare suicidal ideation and behaviour event rates with brodalumab. Please provide further details and results of this review.

Psychiatric adverse events and suicidal ideation are areas of concern for therapies in the treatment of plaque psoriasis. They are common comorbidities in patients with plaque psoriasis and are often excluded from RCTs. Patients with suicidal ideation and behaviour (SIB) risk factors were not specifically excluded from the brodalumab clinical trials.

In light of the data on SIB in the AMAGINE studies, a comparative analysis was performed by Valeant Pharmaceuticals, using data from recent regulatory submissions in plaque psoriasis, to establish the relative risks with brodalumab compared to recently approved agents.

This analysis was compiled by Valeant Pharmaceuticals and submitted to the US Food and Drug Administration (FDA) as part of the submission process. It is publicly available on the FDA website (https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/dermatologicandophthalmicdrugsadvisorycommittee/ucm511360.pdf)

The relevant section is on page 81 onwards.

In summary, the rates of SIB reported in regulatory review documents from clinical trial programmes of recently approved agents for psoriasis include apremilast and anti-IL-17A agents, secukinumab, and ixekizumab were compared to the data in the brodalumab programme.

It was shown that the rates of completed suicide from these development programs are consistent with those seen in the brodalumab program. Rates of attempted suicide in the brodalumab program are similar to those seen in the ixekizumab program, but there is variability across different programmes.

It was concluded that the evidence does not support a causal association between brodalumab and SIB.

A3. Please provide further information on the advisory board meetings (e.g. for estimating discontinuation, referred to on page 120), such as meeting minutes and names of clinicians involved.

The advisory board meeting summary has been uploaded as an attachment to NICEDocs. As the advisory board is confidential, we would need permission from the delegates before we disclose their names. We have listed their roles in the interim. Can you clarify if you still need individual names?

Systematic review

A4. Priority Question: It is unclear whether eligibility criteria stated in the appendices are for the Systematic Literature Review (SLR) or Network Meta-analysis (NMA). Please clarify whether the eligibility criteria presented in tables 78 and 79 are for the NMA (including trials of the different systemic therapies) or for the review of brodalumab studies included in the submission (Document B). Should the title of table 78 be 'Eligibility criteria for biologics and apremilast NMA study selection' and table 79 'Eligibility criteria for DMF NMA study selection'? If these are criteria for the NMA, please present details of the eligibility criteria for the SLR.

Table 78 and Table 79 present the eligibility criteria for the SLR and the NMA, with some additional criteria for the NMA described in D.1.1.5 of Appendix D. The searches and study selection criteria aimed to identify published RCTs of brodalumab as well as published studies of comparators defined in the final scope. The SLRs of brodalumab, biologics, apremilast and DMF used broader inclusion criteria than the NMA, namely in terms of outcomes. The results of the SLR as a whole were assessed to see what outcomes could be feasibly and appropriately synthesised by NMA. PASI responses were the most consistently reported outcomes across the RCTs, have been synthesised in all previous NICE STAs in psoriasis and were necessary to inform efficacy inputs for the economic model.

A5. Priority Question: The ERG have identified a placebo-controlled RCT of brodalumab (Papp et al., NEJM 2012) that was not included in the SLR/submission (although it was included in the NMA). Please explain why this trial was not described in the submission. Please confirm that there are no other relevant RCTs.

The Papp study was a small dose finding phase 2 study with only 40 patients on the licensed dose. The submission focussed on describing the larger phase 3 studies

due to space constraints. Both Papp *et al.* (2012)[1] and Nakagawa *et al.* (2016)[2], a phase II study of brodalumab in 151 Japanese psoriasis patients, were included in the NMA, but not described in B.2. As far as we are aware there are no other relevant studies of brodalumab in plaque psoriasis.

A summary of the Phase II study (published as Papp et al. Brodalumab, an anti-interleukin-17-receptor for psoriasis.(2012) New England Journal of Medicine 366;13;1181:1189) is provided below.

Study design

This was a randomised, double-blind, placebo-controlled, dose-ranging study. Patients were randomly assigned to receive placebo, or brodalumab at 70mg, 140mg, or 210mg administered subcutaneously (sc) on day 1 and at weeks 1, 2 , 4, 6, 8 and 10, or at a dose of 280mg administered sc on day 1 and at weeks 4 and 8. All patients who remained in the study completed an additional visit at week 16 for efficacy and safety assessments (n=188 completed week 16, of a total randomised 198 patients).

Primary efficacy evaluation was percentage improvement in PASI score at week 12. Secondary efficacy evaluations included percentages of patients with a 50%, 75% 90% and 100% improvement from baseline in PASI score, percentage body surface area (BSA) affected, and the static Physician's Global Assessment score. DLQI and SF-36 were patient-reported outcomes used.

A biopsy substudy using tissue from 20 patients was also conducted and the data is presented in the published paper, so we have focussed on presenting the key clinical findings here.

Baseline characteristics

Patients aged 18 to 70 years with stable plaque psoriasis ≥6 months, who were candidates for phototherapy or systemic psoriasis therapy were recruited to the study.

Summary of baseline characteristics - 66% of patients were male, mean age was 43 years, mean 24% BSA affected, mean PASI was 19, mean duration of psoriasis was 19 years. Percentage of patients with severe psoriasis (by sPGA) was 26% in the placebo group and 36-48% in the brodalumab groups. In the combined brodalumab groups 96% had received prior topical treatments and 78% had received prior systemic therapy, compared to 90% and 71% in the placebo group respectively. Full baseline characteristics are available in Table 1 in the published paper.

Results

The mean percentage improvement in PASI score at week 12 was significantly greater in all the brodalumab groups than placebo. Clinical improvements relative to placebo were seen at 2 weeks in the brodalumab groups, and mean improvement in PASI score was similar regardless of whether patients had received prior biologic therapy. Patients receiving brodalumab had a significant decrease in %BSA affected by psoriasis compared to placebo. A significantly higher percentage of patients receiving brodalumab were assessed as being clear of psoriasis using the sPGA measure and DLQI scores were significantly lower compared to patients receiving placebo.

A6. Table 80 (Appendix) presents a list of studies excluded from the NMA with reasons for exclusion. Is a similar table available for studies excluded from the SLR with reasons for exclusion?

Please see separate document "SLR exclusion rationale" for a table with studies excluded from the SLR along with reasons for their exclusion.

A7. Table 80 states a reason for exclusion from NMA as 'secondary publication reporting outcomes other than PASI', however, several non-PASI outcomes were listed as inclusion criteria in tables 78 and 79. Please justify the exclusion of non-PASI outcomes.

The feasibility of meta-analysing outcomes other than PASI, by means of NMA, was assessed. Though the NICE final scope outlined additional outcomes of interest, it was not possible to include all these in the NMA due to gaps in data reported across trials and/or the differences in the way outcomes were reported across trials. The severity of psoriasis measured by PASI response is the most commonly reported outcome in psoriasis trials and therefore this outcome was considered the most appropriate for comparison of efficacy and for use in the cost-effectiveness model. This is consistent with all previous NICE STA submissions in psoriasis.

AMAGINE trials

A8. Please confirm how many patients in each treatment arm in the AMAGINE trials were from the UK.

None. No UK centres were included in the AMAGINE study programmes. Trials centres were in the USA, Canada, Australia and the EU.

A9. Priority Question: On page 41 of the company submission, it states that 'For 12-week analyses of PASI, sPGA, PSI and PSSI (AMAGINE-1 only) response rates, missing data were imputed by non-responder imputation (NRI) for dichotomous endpoints (40, 41) […] For analyses of all other patients during the maintenance phase, missing values for dichotomous endpoints were imputed by NRI, unless otherwise specified; continuous variables were imputed using LOCF.' Please provide additional details; for example, how many values were imputed for:

a. **each treatment group**

b. **each outcome**

c. **each timepoint?**

Table 1: Illustrates the number of missing values for the endpoints PASI, sPGA, PSI and PSSI (AMAGINE-1) at week 12 for all patients.

	AMAGINE-1	AMAGINE-2	AMAGINE-3

	Brodalumab 210 mg Q2W	Placebo	Brodalumab 210 mg Q2W	Placebo	Ustekinumab	Brodalumab 210 mg Q2W	Placebo	Ustekinumab
PASI, OBS/NRI (%diff)	212/222 (4.50%)	209/220 (5.00%)	593/612 (3.10%)	299/309 (3.24%)	290/300 (3.33%)	605/624 (3.04%)	300/315 (4.76%)	302/313 (3.51%)
sPGA, OBS/NRI (%diff)	212/222 (4.50%)	209/220 (5.00%)	593/612 (3.10%)	298/309 (3.56%)	290/300 (3.33%)	605/624 (3.04%)	300/315 (4.76%)	302/313 (3.51%)
PSI, OBS/NRI (%diff)	201/222 (9.46%)	202/220 (8.18%)	552/612 (9.80%)	278/309 (10.03%)	275/300 (8.33%)	556/624 (10.90%)	282/315 (10.48%)	283/313 (9.58%)
PSSI, OBS/NRI (%diff)	81/82 (1.22%)	90/95 (5.26%)						
Each cell contains the number of observed values, the NRI values and in brackets the percentage of missing values. As illustrated by the table the number of missing values are comparable across studies and treatment groups for each endpoint.								

Table 2: Illustrates the number of missing values for each endpoint at week 52

	AMAGINE-2		**AMAGINE-3**	
	Brodalumab 210 mg Q2W	Ustekinumab*)	Brodalumab 210 mg Q2W	Ustekinumab*)
PASI, OBS/NRI (%miss)	113/168 (32.74%)	144/289 (50.17%)	111/171 (35.09%)	150/301 (50.17%)
sPGA, OBS/NRI (%miss)	113/168 (32,74%)	144/289 (50.16%)	111/171 (35.09%)	150/301 (50.17%)
PSI, OBS/NRI (%miss)	95/168 (43,45%)	129/289 (55.36%)	85/171 (50.29%)	131/301 (56.48%)
*) Please notice that treatment groups are defined as planned treatment for induction / maintenance phases so patient on rescue or treatment change on Ustekinumab will be considered as missing in the above numbers				

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

A10. The EMA report refers to a subgroup analysis based on weight (≤100kg vs. >100kg.). Please provide results for this analysis. Are there any additional subgroup analyses that were performed, but not reported in the submission?

All subgroup analyses are reported in the clinical study reports for AMAGINE 2 and 3, in Table 10.4.

The following subgroup analyses were performed

- severity of psoriasis (PASI < 20 or ≥ 20 [all patients had baseline PASI > 10])
- severity of psoriasis (DLQI ≤ 10, > 10 or missing)
- previous use of systemic non-biological therapy or phototherapy (yes or no)
- previous use of systemic non-biological therapy (yes or no)
- number of previous systemic non-biological therapies (0, 1 or ≥ 2)
- non-biological systemic agent failure or contraindication (yes or no)
- previous use of psoriasis biological therapy (yes or no)
- previous failure of psoriasis biological therapy (yes or no)
- previous use of anti-TNF therapy (yes or no)
- concomitant use of topical therapy (yes or no)
- baseline total body weight (≤100kg, >100kg)
- geographic region
- age (< 65, ≥ 65)
- sex

No significant differences were seen in any subgroup analysis apart from baseline body weight.

The weight-based analysis is referred to in the company submission. As weight based dosing is outside the licence for brodalumab the results were not provided in detail.

Baseline body weight subgroup analysis

For AMAGINE 2 the key findings of the weight based subgroup analysis were reported as follows (AMAGINE-2 CSR):

Response rates in brodalumab subjects for sPGA (0 or 1), PASI 75, and PASI 100 at week 12 were lower in subgroups of subjects who had a baseline body weight of > 100 kg (n=854) compared with subjects who had a baseline body weight of ≤ 100 kg (n=368).

Response rates for sPGA (0 or 1) for subjects in the brodalumab 210 mg Q2W group were 66.8% for subjects > 100 kg at baseline (n=184) and 83.6% for subjects ≤ 100

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

kg at baseline (n=428). For subjects in the brodalumab 140 mg Q2W group, response rates were 31.0%, > 100 kg (n=184) and 69.7%, ≤ 100 kg (n=426).

Response rates for PASI 75 for subjects in the brodalumab 210 mg Q2W group were 76.6% for subjects > 100 kg at baseline (n=184) and 90.4% for subjects ≤ 100 kg at baseline(n=428). For subjects in the brodalumab 140 mg Q2W group, response rates were 41.8%, > 100 kg (n=184) and 77.2%, ≤ 100 kg (n=426).

Response rates for PASI 100 for subjects in the brodalumab 210 mg Q2W group were 33.7% for subjects > 100 kg at baseline (n=184) and 49.1% for subjects ≤ 100 kg at baseline (n=428). For subjects in the brodalumab 140 mg Q2W group, response rates were 7.6%, > 100 kg (n=184) and 33.6%, ≤ 100 kg (n=428).

For AMAGINE 3 the key findings of the weight based subgroup analysis were reported as follows (AMAGINE-3 CSR):

Among subjects ≤ 100 kg at baseline, 88.2% of subjects in the 210 Q2W group (n=462), 77.3% of subjects in the 140 mg Q2W group (n=458), and 6.0% of subjects in the placebo group (n=233) achieved a 75% improvement in PASI at week 12.

Among subjects > 100 kg at baseline, 76.5% of subjects in the 210 Q2W group (n=166), 46.7% of subjects in the 140 mg Q2W group (n=167) and 6.1% of subjects in the placebo group (n=82) achieved a 75% improvement in PASI at week 12. The nominal p-values < 0.001 for the response rates for both doses compared with placebo in both subgroups. Similar differences in response rates between the 2 brodalumab doses and placebo were seen for the other week 12 endpoints.

In summary, treatment with 210 mg Q2W or 140 mg Q2W in subjects with baseline total body weight ≤ 100 kg resulted in consistently higher response rates for the co-primary endpoints at week 12 than in subjects with baseline weight > 100kg. In both weight subgroups, higher response rates were observed in subjects treated with 210 mg Q2W than in subjects treated with 140 mg Q2W.

A11. Priority Question: Tables 121-123 (Appendix) report reasons that patients discontinued from the AMAGINE studies. Please provide further information about the categories 'full consent withdrawn' and 'other', because these make up the majority of patients who discontinued.

The treatment arms in **Table *3*** reflects the treatment arm at the time of withdrawal.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Table 3. Further information regarding categories of ”full consent withdrawn” and ”other” in AMAGINE clinical trials

				[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]	[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]	[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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

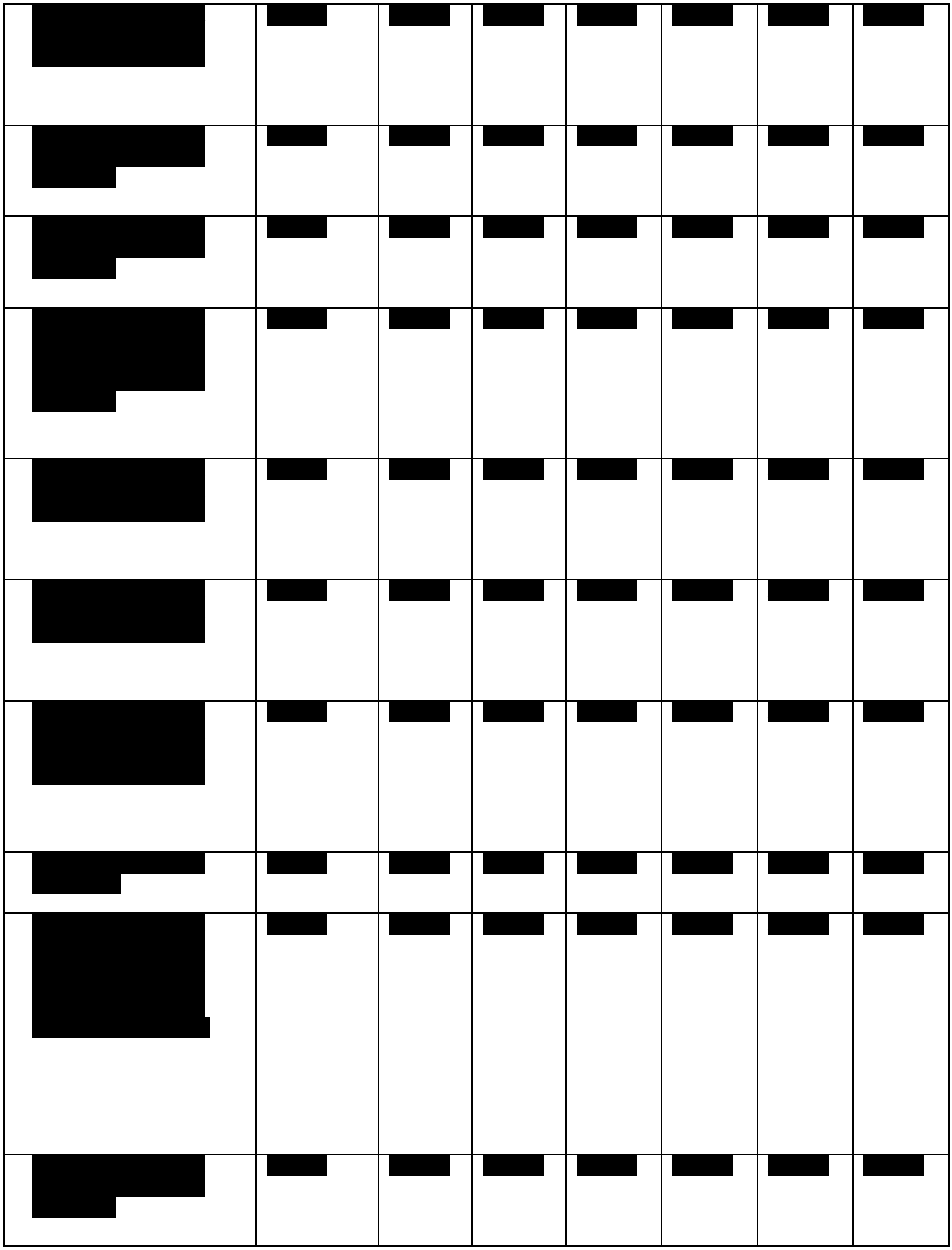
+44 (0)300 323 0140

[redacted]

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140



NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

[redacted]

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

[redacted]

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

[redacted]

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

[redacted]

NICE National Institute for Health and Care Excellence

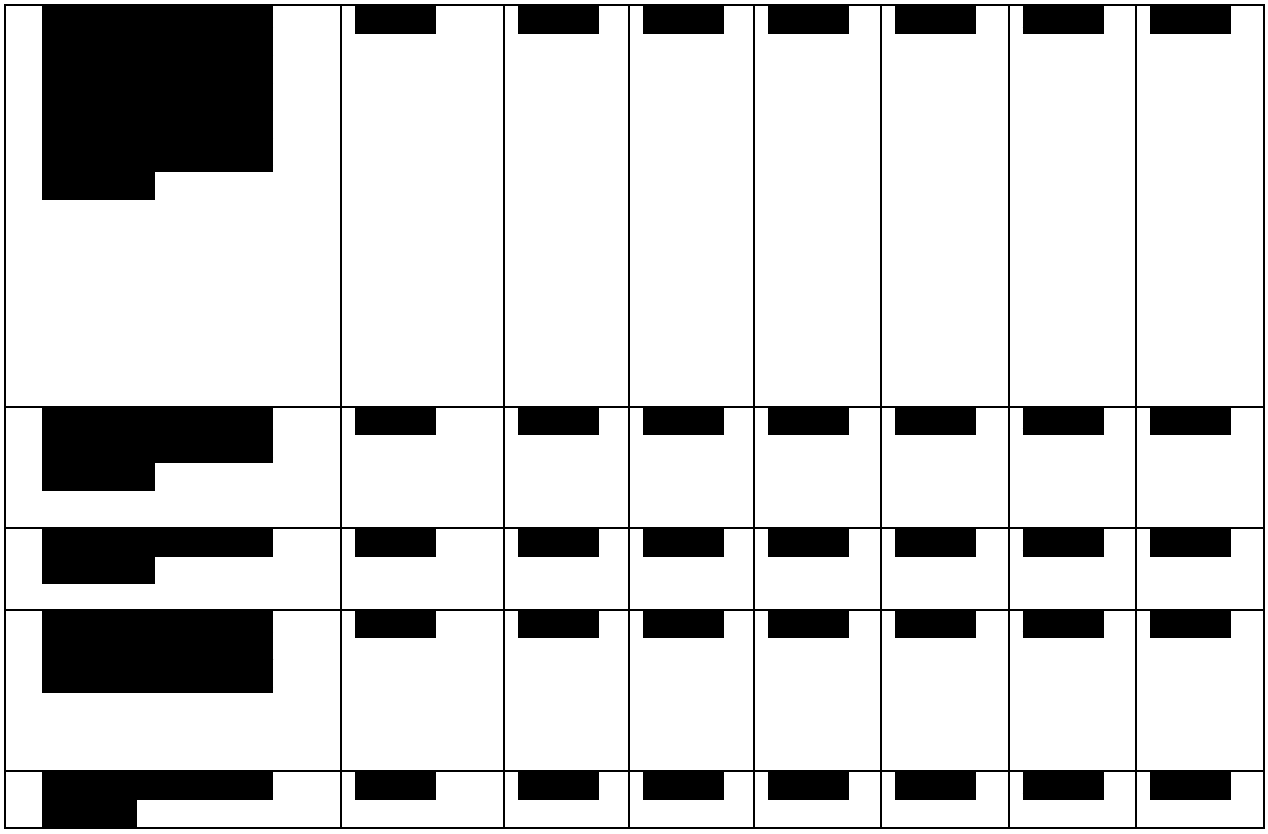
10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140



A12. Priority Question: Please add data on the number of patients included in analyses at each timepoint for Figures 6-11, 13-15, 19-20 and 24.

Figures 6-11, 15, 19, 20

The patient numbers at each time point for the figures requested are listed below. This is the full analysis set (FAS) described in table 10 and since this is a non-responder imputation analysis (NRI) the patient numbers will be the same at each time point and on each figure.

Patient numbers from Full Analysis Set (FAS) for AMAGINE-2 and 3.

	Placebo	Brodalumab 210mg Q2W	Ustekinumab
AMAGINE-2	309	612	300
AMAGINE-3	315	624	313

For Figure 13, the n numbers are in the table below for the efficacy analysis set (EAS).

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

	Ustekinumab	Brodalumab 210mg Q2W
AMAGNE-2	289	334
AMAGINE-3	301	342

Figure 14
This is the efficacy analysis of patients on continuous treatment with brodalumab 210mg Q2W throughout the study. The n numbers are listed on the figures and are the same at each time point (NRI analysis).

Figure 24
In the EQ-5D utility score analysis in AMAGINE-1, the n numbers at baseline were placebo, n= 216; brodalumab 210mg Q2W, n = 221.

A13. Table 16 presents the proportion of patients receiving rescue therapy in AMAGINE-2 and AMAGINE-3. Patients in the ustekinumab group could receive rescue therapy with brodalumab or ustekinumab; please clarify whether patients were randomly assigned to these rescue therapies?

The identical protocols for AMAGINE-2 and 3 defined rescue therapy procedures for patients not responding to therapy.

- Subjects qualify for rescue treatment at or after week 16 with an inadequate response (defined as a single sPGA of ≥3 or persistent sPGA values of 2 over at least a 4-week period). Through week 52, subjects can only qualify for rescue treatment at scheduled visits. Rescue treatment was blinded.

- At week 16, any subject in the study who has an inadequate response is eligible for rescue with 210 mg brodalumab, regardless of treatment arm. After week 16 but before week 52, subjects on brodalumab who qualify for rescue will receive 210 mg Q2W brodalumab; subjects on ustekinumab will continue to receive ustekinumab
- Subjects who qualify for rescue at and after week 52 will receive 210 mg Q2W brodalumab

A14. Table 24 includes patients treated with other doses of brodalumab or with ustekinumab, in the maintenance phase before changing to brodalumab 210 mg every 2 weeks in the open-label extension phase. Please provide subgroup data for patients who received brodalumab 210 mg every 2 weeks during the maintenance phase (i.e. excluding patients who received lower doses of brodalumab or who received ustekinumab during the maintenance phase).

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

At week 52, patients treated with ustekinumab in AMAGINE-2 and AMAGINE-3 were switched to receive brodalumab 210 mg Q2W during the open-label extension phase. Patients receiving brodalumab continued to receive brodalumab at the same maintenance or rescue dose (49, 50). Similarly, patients receiving brodalumab in AMAGINE-1 continued to receive brodalumab at the same maintenance or rescue dose (45). PASI and sPGA responses for long-term extension phase participants are summarised in Table 24A.

[redacted] Extension phase data are as observed, with no imputation; since a number of patients were lost to follow-up (particularly in AMAGINE-2) these observations should be treated with caution.

Table 24A Summary of PASI and sPGA responses during open-label long-term extension phase (as observed) / All maintenance therapies

	Week	Brodalumab 210 mg Q2W		
		AMAGINE-1 (N = 470)	AMAGINE-2 (N = 1392)	AMAGINE-3 (N = 1403)
PASI endpoints				
PASI 75	52	[redacted]	[redacted]	[redacted]
	108	[redacted]	[redacted]	[redacted]
	120	[redacted]	[redacted]	[redacted]
PASI 90	52	[redacted]	[redacted]	[redacted]
	108	[redacted]	[redacted]	[redacted]
	120	[redacted]	[redacted]	[redacted]
PASI 100	52	[redacted]	[redacted]	[redacted]
	108	[redacted]	[redacted]	[redacted]
	120	[redacted]	[redacted]	[redacted]
sPGA endpoints				
sPGA response (0 or 1)	52	[redacted]	[redacted]	[redacted]
	108	[redacted]	[redacted]	[redacted]
	120	[redacted]	[redacted]	[redacted]
sPGA 0	52	[redacted]	[redacted]	[redacted]
	108	[redacted]	[redacted]	[redacted]
	120	[redacted]	[redacted]	[redacted]

All data are n/N (%). Data are as observed, with no imputation.
52-week data include patients treated with other doses of brodalumab, or with ustekinumab up to week 52 before changing to brodalumab 210 mg Q2W in the open-label extension phase.
PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: Long-term extension phase CSRs: AMAGINE-1 (45), AMAGINE-2 (49) and AMAGINE-3 (50).

Below in Table 24B is summarized patient at brodalumab 210 mg Q2W during both the maintenance and the open-label extension phase and during Maintenance phase (Week 12-52).

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Compared to Table 24A patients from AMAGINE 1 at placebo or Brodalumab 140 mg Q2 as maintenance therapy are excluded in the below analyses, and for AMAGINE 2+3 patients on Ustekinumab and Brodalumab 14 mg (Q2, Q4 and Q8) in maintenance phase are excluded below compared to Table 24A.

Table 24B Summary of PASI and sPGA responses during open-label long-term extension phase (as observed) / Only Brodakumab 210 mg Q2 as maintenance therapy

	Week	Brodalumab 210 mg Q2W		
		AMAGINE-1 (N = 371)	AMAGINE-2 (N = 581)	AMAGINE-3 (N = 584)
PASI endpoints				
PASI 75	52	[redacted]	[redacted]	[redacted]
	108	[redacted]	[redacted]	[redacted]
	120	[redacted]	[redacted]	[redacted]
PASI 90	52	[redacted]	[redacted]	[redacted]
	108	[redacted]	[redacted]	[redacted]
	120	[redacted]	[redacted]	[redacted]
PASI 100	52	[redacted]	[redacted]	[redacted]
	108	[redacted]	[redacted]	[redacted]
	120	[redacted]	[redacted]	[redacted]
sPGA endpoints				
sPGA response (0 or 1)	52	[redacted]	[redacted]	[redacted]
	108	[redacted]	[redacted]	[redacted]
	120	[redacted]	[redacted]	[redacted]
sPGA 0	52	[redacted]	[redacted]	[redacted]
	108	[redacted]	[redacted]	[redacted]
	120	[redacted]	[redacted]	[redacted]

All data are n/N (%). Data are as observed, with no imputation.
These analyses include patients only at brodalumab 210 mg Q2 both during maintenance and the open-label extension phase.
PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: New analyses based on Long-term extension phase CSRs: AMAGINE-1 (45), AMAGINE-2 (49) and AMAGINE-3 (50).

A15. Please provide further information on the [redacted] deaths that occurred during the open-label extension of AMAGINE-2 and AMAGINE-3, (page 84). Page 84 directs readers to section B.2.10.3.1, which refers to Appendix F Tables 102-104. However, Tables 102-104 only report [redacted] fatal adverse events.

Table 102 in the NICE submission reports deaths that occurred during exposure to brodalumab ([redacted] death in the AMAGINE 2 OLE and [redacted] deaths in the AMAGINE 3 OLE), but does not report deaths that occurred during the open label extensions after the end of exposure. The end of exposure was defined as 14 days after last dose of brodalumab 210 mg Q2W.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

The details of the deaths that occurred in the open-label extensions of AMAGINE 2 and 3 are as follows:

AMAGINE 2:

The [redacted] deaths that occurred during the AMAGINE 2 OLE are described below (p56 AMAGINE 2 LTE abbreviated CSR):

[redacted]

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

[redacted]

AMAGINE 3:

The deaths that occurred during the AMAGINE 3 open-label extension are described below (p54 AMAGINE 3 LTE abbreviated CSR):

[redacted]

Network Meta-Analysis

A16. Please give further details of why Krueger (2007) (a human interleukin-12/23 monoclonal antibody for the treatment of psoriasis NCT00320216) was excluded from the network meta-analysis.

The dosing schedule for ustekinumab in this study was not aligned with the label (i.e. doses at week 0, 4 and every 12 weeks thereafter). In Krueger *et al.* (2007)[3], patients were randomised to placebo or one of 4 ustekinumab dosing schedules: one 45-mg dose, one 90-mg dose, four weekly 45-mg doses, or four weekly 90-mg doses).

A17. Please provide pairwise comparisons of the relative risk (with 95% credible interval) of achieving a PASI ≥75 response for all interventions in the base case NMA.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Please see **Table *4***, which presents the relative risk (with 95% credible interval) of achieving a PASI ≥75 response for all pairwise comparisons from the base case NMA.

Table 4. Median risk ratio (95% credible interval) for all pairwise comparisons on PASI 75 response (base case)

BRO 140																			
[redacted]	BRO 210																		
[redacted]	[redacted]	ADA	0.29 (0.2, 0.4)	0.41 (0.33, 0.51)	0.59 (0.5, 0.7)	0.81 (0.73, 0.9)	1.2 (1.09, 1.33)	1.31 (1.21, 1.45)	1.37 (1.26, 1.51)	1.1 (0.99, 1.23)	1.27 (1.16, 1.4)	1.08 (0.98, 1.21)	1.14 (1.03, 1.27)	1.08 (0.97, 1.2)	0.29 (0.18, 0.45)	0.37 (0.23, 0.54)	0.54 (0.41, 0.67)	0.38 (0.18, 0.66)	0.09 (0.07, 0.1)
[redacted]	[redacted]	3.4 (2.49, 4.88)	APR 20	1.41 (1.04, 1.97)	2.02 (1.46, 2.91)	2.75 (2.03, 3.94)	4.08 (2.98, 5.9)	4.48 (3.27, 6.48)	4.66 (3.4, 6.75)	3.74 (2.73, 5.4)	4.31 (3.15, 6.23)	3.69 (2.7, 5.31)	3.89 (2.84, 5.6)	3.66 (2.68, 5.27)	1 (0.56, 1.71)	1.24 (0.73, 2.08)	1.84 (1.24, 2.77)	1.28 (0.58, 2.43)	0.3 (0.22, 0.42)
[redacted]	[redacted]	2.41 (1.97, 3.02)	0.71 (0.51, 0.96)	APR 30	1.43 (1.15, 1.81)	1.95 (1.62, 2.43)	2.9 (2.36, 3.65)	3.18 (2.6, 3.99)	3.31 (2.7, 4.17)	2.65 (2.17, 3.33)	3.06 (2.5, 3.85)	2.62 (2.14, 3.28)	2.76 (2.26, 3.46)	2.6 (2.12, 3.26)	0.71 (0.42, 1.12)	0.88 (0.55, 1.35)	1.31 (0.95, 1.76)	0.91 (0.43, 1.62)	0.21 (0.17, 0.26)
[redacted]	[redacted]	1.68 (1.43, 2.01)	0.5 (0.34, 0.68)	0.7 (0.55, 0.87)	ETA 50	1.36 (1.19, 1.58)	2.02 (1.72, 2.41)	2.22 (1.9, 2.63)	2.31 (1.98, 2.75)	1.85 (1.58, 2.2)	2.14 (1.83, 2.54)	1.83 (1.56, 2.17)	1.92 (1.64, 2.28)	1.81 (1.55, 2.15)	0.49 (0.29, 0.77)	0.62 (0.38, 0.93)	0.91 (0.67, 1.19)	0.64 (0.3, 1.09)	0.15 (0.12, 0.18)
[redacted]	[redacted]	1.24 (1.11, 1.37)	0.36 (0.25, 0.49)	0.51 (0.41, 0.62)	0.73 (0.63, 0.84)	ETA 100	1.48 (1.34, 1.64)	1.62 (1.5, 1.78)	1.69 (1.56, 1.85)	1.36 (1.24, 1.49)	1.57 (1.44, 1.72)	1.34 (1.22, 1.47)	1.41 (1.29, 1.55)	1.33 (1.21, 1.47)	0.36 (0.22, 0.56)	0.45 (0.28, 0.67)	0.67 (0.5, 0.84)	0.47 (0.22, 0.8)	0.11 (0.09, 0.12)
[redacted]	[redacted]	0.83 (0.75, 0.92)	0.25 (0.17, 0.34)	0.35 (0.27, 0.42)	0.49 (0.41, 0.58)	0.68 (0.61, 0.75)	INF	1.1 (1.02, 1.19)	1.14 (1.07, 1.24)	0.92 (0.83, 1.01)	1.06 (0.98, 1.15)	0.9 (0.82, 0.99)	0.95 (0.87, 1.05)	0.9 (0.81, 0.99)	0.24 (0.15, 0.38)	0.3 (0.19, 0.45)	0.45 (0.35, 0.56)	0.31 (0.15, 0.55)	0.07 (0.06, 0.09)
[redacted]	[redacted]	0.76 (0.69, 0.83)	0.22 (0.15, 0.31)	0.31 (0.25, 0.38)	0.45 (0.38, 0.53)	0.62 (0.56, 0.67)	0.91 (0.84, 0.98)	IXE Q4W	1.04 (1.01, 1.08)	0.84 (0.77, 0.9)	0.96 (0.91, 1.02)	0.83 (0.76, 0.89)	0.87 (0.8, 0.93)	0.82 (0.75, 0.88)	0.22 (0.13, 0.34)	0.28 (0.17, 0.41)	0.41 (0.31, 0.52)	0.29 (0.13, 0.5)	0.07 (0.05, 0.08)
[redacted]	[redacted]	0.73 (0.66, 0.79)	0.21 (0.15, 0.29)	0.3 (0.24, 0.37)	0.43 (0.36, 0.51)	0.59 (0.54, 0.64)	0.88 (0.81, 0.94)	0.96 (0.93, 0.99)	IXE Q2W	0.8 (0.74, 0.86)	0.93 (0.88, 0.97)	0.79 (0.73, 0.85)	0.83 (0.77, 0.89)	0.79 (0.72, 0.84)	0.21 (0.13, 0.33)	0.27 (0.17, 0.4)	0.4 (0.3, 0.5)	0.28 (0.13, 0.48)	0.06 (0.05, 0.08)
[redacted]	[redacted]	0.91 (0.81, 1.01)	0.27 (0.19, 0.37)	0.38 (0.3, 0.46)	0.54 (0.45, 0.63)	0.74 (0.67, 0.81)	1.09 (0.99, 1.2)	1.2 (1.11, 1.3)	1.25 (1.16, 1.35)	SEC 150	1.15 (1.09, 1.23)	0.99 (0.9, 1.08)	1.04 (0.95, 1.14)	0.98 (0.89, 1.07)	0.27 (0.16, 0.41)	0.33 (0.21, 0.49)	0.49 (0.37, 0.62)	0.34 (0.16, 0.59)	0.08 (0.07, 0.09)
[redacted]	[redacted]	0.79 (0.71, 0.86)	0.23 (0.16, 0.32)	0.33 (0.26, 0.4)	0.47 (0.39, 0.55)	0.64 (0.58, 0.69)	0.95 (0.87, 1.02)	1.04 (0.98, 1.1)	1.08 (1.03, 1.14)	0.87 (0.81, 0.91)	SEC 300	0.86 (0.79, 0.92)	0.9 (0.83, 0.97)	0.85 (0.78, 0.91)	0.23 (0.14, 0.36)	0.29 (0.18, 0.43)	0.43 (0.32, 0.54)	0.3 (0.14, 0.51)	0.07 (0.06, 0.08)
[redacted]	[redacted]	0.92 (0.83, 1.02)	0.27 (0.19, 0.37)	0.38 (0.3, 0.47)	0.55 (0.46, 0.64)	0.75 (0.68, 0.82)	1.11 (1.01, 1.22)	1.21 (1.13, 1.32)	1.26 (1.18, 1.37)	1.01 (0.92, 1.11)	1.17 (1.08, 1.27)	UST 45	1.05 (0.99, 1.12)	0.99 (0.9, 1.09)	0.27 (0.16, 0.42)	0.34 (0.21, 0.5)	0.5 (0.37, 0.63)	0.35 (0.16, 0.6)	0.08 (0.07, 0.1)
[redacted]	[redacted]	0.88 (0.79, 0.97)	0.26 (0.18, 0.35)	0.36 (0.29, 0.44)	0.52 (0.44, 0.61)	0.71 (0.65, 0.78)	1.05 (0.96, 1.15)	1.15 (1.07, 1.25)	1.2 (1.12, 1.3)	0.96 (0.88, 1.06)	1.11 (1.03, 1.2)	0.95 (0.89, 1.01)	UST 90	0.94 (0.86, 1.04)	0.26 (0.15, 0.4)	0.32 (0.2, 0.47)	0.47 (0.36, 0.6)	0.33 (0.16, 0.57)	0.08 (0.06, 0.09)
[redacted]	[redacted]	0.93 (0.83, 1.03)	0.27 (0.19, 0.37)	0.39 (0.31, 0.47)	0.55 (0.46, 0.65)	0.75 (0.68, 0.83)	1.12 (1.01, 1.23)	1.22 (1.13, 1.33)	1.27 (1.19, 1.38)	1.02 (0.93, 1.12)	1.18 (1.1, 1.27)	1.01 (0.92, 1.11)	1.06 (0.97, 1.17)	UST label	0.27 (0.16, 0.42)	0.34 (0.21, 0.5)	0.5 (0.38, 0.64)	0.35 (0.16, 0.61)	0.08 (0.07, 0.1)
[redacted]	[redacted]	3.41 (2.21, 5.71)	1 (0.58, 1.77)	1.41 (0.89, 2.39)	2.03 (1.29, 3.41)	2.76 (1.8, 4.61)	4.1 (2.65, 6.87)	4.49 (2.91, 7.55)	4.68 (3.03, 7.87)	3.75 (2.43, 6.31)	4.33 (2.81, 7.28)	3.7 (2.4, 6.22)	3.9 (2.53, 6.55)	3.67 (2.38, 6.16)	DMF	1.25 (0.86, 1.83)	1.85 (1.12, 3.19)	1.29 (0.55, 2.68)	0.3 (0.19, 0.49)
[redacted]	[redacted]	2.73 (1.85, 4.36)	0.8 (0.48, 1.37)	1.13 (0.74, 1.83)	1.62 (1.08, 2.61)	2.21 (1.5, 3.53)	3.28 (2.21, 5.25)	3.6 (2.43, 5.78)	3.75 (2.53, 6.02)	3 (2.03, 4.81)	3.47 (2.34, 5.57)	2.97 (2.01, 4.75)	3.12 (2.11, 4.99)	2.94 (1.99, 4.71)	0.8 (0.55, 1.16)	FUM	1.48 (0.93, 2.43)	1.03 (0.45, 2.09)	0.24 (0.16, 0.38)
[redacted]	[redacted]	1.85 (1.48, 2.41)	0.54 (0.36, 0.81)	0.76 (0.57, 1.05)	1.09 (0.84, 1.49)	1.49 (1.19, 1.98)	2.21 (1.8, 2.88)	2.43 (1.93, 3.24)	2.53 (2, 3.38)	2.03 (1.6, 2.71)	2.34 (1.86, 3.13)	2 (1.59, 2.67)	2.11 (1.67, 2.82)	1.99 (1.57, 2.65)	0.54 (0.31, 0.89)	0.8 (0.55, 1.16)	MTX	0.7 (0.32, 1.28)	0.16 (0.13, 0.21)
[redacted]	[redacted]	2.65 (1.52, 5.63)	0.78 (0.41, 1.72)	1.1 (0.62, 2.35)	1.57 (0.91, 3.3)	2.14 (1.25, 4.51)	3.18 (1.83, 6.8)	3.49 (2.01, 7.43)	3.63 (2.09, 7.76)	2.91 (1.68, 6.18)	3.36 (1.94, 7.17)	2.87 (1.66, 6.12)	3.02 (1.74, 6.44)	2.85 (1.65, 6.06)	0.78 (0.37, 1.8)	0.54 (0.31, 0.89)	1.43 (0.78, 3.11)	ACI	0.23 (0.13, 0.49)
[redacted]	[redacted]	11.45 (9.68, 13.61)	3.36 (2.39, 4.56)	4.74 (3.85, 5.78)	6.79 (5.69, 8.15)	9.27 (8.01, 10.81)	13.74 (11.48, 16.58)	15.08 (12.55, 18.25)	15.71 (13.02, 19.08)	12.59 (10.6, 15.08)	14.53 (12.14, 17.52)	12.43 (10.49, 14.84)	13.08 (10.99, 15.69)	12.32 (10.4, 14.71)	3.35 (2.04, 5.16)	4.18 (2.65, 6.19)	6.2 (4.68, 7.94)	4.32 (2.05, 7.51)	PBO

A18. Priority Question: Please provide additional results from NMA sensitivity analysis 1 (section B.2.9.3.2), which only includes EMA licensed doses that are currently recommended by NICE:

a. Please provide the absolute predicted PASI 75, 90 and 100 responses (with 95% credible interval) for all interventions, i.e., the equivalent of Table 26 for sensitivity analysis 1.

Please see Table 5 for the absolute predicted PASI 75, 90 and 100 responses (with 95% credible intervals) for all interventions from sensitivity analysis 1.

Table 5. Predicted PASI responses for evaluated interventions – sensitivity analysis 1

Treatment	Probability of PASI response, median (95% CrI)			
	PASI 50	PASI 75	PASI 90	PASI 100
Placebo	14.6% (12.2-17.3)	5.5% (4.3-6.9)	1.2% (0.9-1.6)	0.1% (0.1-0.2)
Brodalumab 210mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg Q2W	81.3% (75.9-85.8)	63.4% (56.3-70.1)	37.7% (30.9-44.8)	13.1% (9.5-17.4)
Apremilast 30mg BID	47% (39.3-54.6)	26.8% (20.7-33.5)	10.1% (7-13.9)	1.9% (1.1-2.9)
Etanercept 50 mg / week	62.6% (54.6-70.3)	41.2% (33.4-49.5)	19% (13.9-25.2)	4.6% (2.9-7)
Infliximab 5mg/kg	93.1% (89.1-95.9)	82.6% (75.5-88.3)	61.2% (51.3-70.3)	30% (21.8-39.1)
Ixekizumab 80mg Q2W	96.4% (94.4-97.7)	89.4% (85.2-92.7)	72.4% (65.1-78.8)	41.5% (33.7-49.6)
Secukinumab 300mg	93.5% (90.7-95.7)	83.4% (78.2-87.9)	62.4% (54.9-69.7)	31.1% (24.6-38.4)
Ustekinumab 45mg	87.6% (83.1-91.1)	72.9% (66-78.9)	48.1% (40.4-55.8)	19.6% (14.6-25.4)
Ustekinumab 90mg	90% (85.7-93.1)	76.9% (70-82.7)	53.1% (44.7-61.2)	23.3% (17.3-30)
Ustekinumab (in-label dose)	85.9% (81.4-89.7)	70.2% (63.5-76.4)	45% (37.8-52.6)	17.5% (13.1-22.8)
DMF	36.5% (24.6-50)	18.7% (10.9-29.3)	6.1% (2.9-11.5)	0.9% (0.3-2.2)

BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks.

b. Please provide pairwise comparisons of the relative risk (with 95% credible interval) of achieving a PASI ≥75 response for all interventions from sensitivity analysis 1.

Please see **Table *6***, which presents the relative risk (with 95% credible interval) of achieving a PASI ≥75 response for all pairwise comparisons from sensitivity analysis 1.

Table 6. Median risk ratio (95% credible interval) for all pairwise comparisons on PASI 75 response (sensitivity analysis 1)

Brodalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	Adalimumab	0.42 (0.33, 0.52)	0.65 (0.53, 0.78)	1.3 (1.16, 1.47)	1.41 (1.28, 1.57)	1.31 (1.19, 1.47)	1.15 (1.03, 1.29)	1.21 (1.09, 1.36)	1.11 (0.99, 1.25)	0.3 (0.17, 0.46)	0.09 (0.07, 0.1)
[redacted]	2.36 (1.92, 3.01)	Apremilast	1.53 (1.22, 1.98)	3.08 (2.48, 3.94)	3.33 (2.7, 4.28)	3.11 (2.52, 3.99)	2.72 (2.2, 3.46)	2.86 (2.32, 3.66)	2.62 (2.13, 3.35)	0.7 (0.41, 1.13)	0.21 (0.17, 0.26)
[redacted]	1.54 (1.28, 1.88)	0.65 (0.5, 0.82)	Etanercept	2 (1.67, 2.46)	2.17 (1.82, 2.65)	2.02 (1.7, 2.47)	1.77 (1.47, 2.16)	1.86 (1.55, 2.28)	1.7 (1.43, 2.08)	0.45 (0.27, 0.72)	0.13 (0.11, 0.16)
[redacted]	0.77 (0.68, 0.86)	0.33 (0.25, 0.4)	0.5 (0.41, 0.6)	Infliximab	1.08 (1.01, 1.18)	1.01 (0.93, 1.11)	0.88 (0.8, 0.98)	0.93 (0.84, 1.03)	0.85 (0.77, 0.95)	0.23 (0.13, 0.35)	0.07 (0.05, 0.08)
[redacted]	0.71 (0.64, 0.78)	0.3 (0.23, 0.37)	0.46 (0.38, 0.55)	0.92 (0.85, 0.99)	Ixekizumab	0.93 (0.88, 0.99)	0.82 (0.74, 0.88)	0.86 (0.79, 0.93)	0.79 (0.72, 0.85)	0.21 (0.12, 0.33)	0.06 (0.05, 0.08)
[redacted]	0.76 (0.68, 0.84)	0.32 (0.25, 0.4)	0.49 (0.4, 0.59)	0.99 (0.9, 1.07)	1.07 (1.01, 1.14)	Secukinumab	0.87 (0.79, 0.95)	0.92 (0.84, 1)	0.84 (0.78, 0.91)	0.22 (0.13, 0.35)	0.07 (0.05, 0.08)
[redacted]	0.87 (0.78, 0.97)	0.37 (0.29, 0.45)	0.57 (0.46, 0.68)	1.13 (1.02, 1.25)	1.23 (1.13, 1.34)	1.14 (1.05, 1.26)	Ustekinumab 45 mg	1.05 (0.99, 1.12)	0.96 (0.87, 1.07)	0.26 (0.15, 0.4)	0.08 (0.06, 0.09)
[redacted]	0.83 (0.73, 0.92)	0.35 (0.27, 0.43)	0.54 (0.44, 0.64)	1.07 (0.97, 1.19)	1.16 (1.08, 1.27)	1.08 (1, 1.19)	0.95 (0.89, 1.01)	Ustekinumab 90 mg	0.91 (0.83, 1.02)	0.24 (0.14, 0.38)	0.07 (0.06, 0.09)
[redacted]	0.9 (0.8, 1.01)	0.38 (0.3, 0.47)	0.59 (0.48, 0.7)	1.18 (1.06, 1.3)	1.27 (1.18, 1.39)	1.19 (1.1, 1.29)	1.04 (0.93, 1.15)	1.09 (0.98, 1.21)	Ustekinumab (per label)	0.27 (0.16, 0.41)	0.08 (0.06, 0.09)
[redacted]	3.39 (2.17, 5.73)	1.43 (0.89, 2.44)	2.2 (1.38, 3.76)	4.4 (2.82, 7.52)	4.78 (3.07, 8.15)	4.45 (2.87, 7.6)	3.89 (2.5, 6.6)	4.1 (2.63, 6.97)	3.75 (2.41, 6.37)	DMF	0.29 (0.19, 0.49)
[redacted]	11.53 (9.61, 13.95)	4.88 (3.9, 6.01)	7.49 (6.08, 9.25)	15.01 (12.23, 18.62)	16.28 (13.21, 20.24)	15.19 (12.42, 18.74)	13.26 (10.95, 16.2)	13.97 (11.49, 17.17)	12.78 (10.6, 15.57)	3.4 (2.05, 5.28)	Placebo

c. **Please provide the results of sensitivity analysis 1 in the form of Convergence Diagnostic and Output Analysis (CODA) for use in the economic model.**

Please see data on tab “SA1” provided in separate SA_Coda_for_CEM.xls

A19. Priority Question: Please provide additional results from NMA sensitivity analysis 4 (section B.2.9.3.2), which excluded studies reporting greater than 30% of randomised patients having previously tried biological therapy:

a. **Please provide the absolute predicted PASI 75, 90 and 100 responses (with 95% credible interval) for all interventions, i.e., the equivalent of Table 26 for sensitivity analysis 4.**

Please see **Table 7** for the absolute predicted PASI 75, 90 and 100 responses (with 95% credible intervals) for all interventions from sensitivity analysis 4.

Table 7 : Predicted PASI responses for evaluated interventions – Sensitivity analysis 4

Treatment	Probability of PASI response, median (95% CrI)			
	PASI 50	PASI 75	PASI 90	PASI 100
Placebo	15.8% (13.1-18.9)	6.3% (4.9-7.9)	1.4% (1-1.9)	0.1% (0.1-0.2)
Brodalumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]
Brodalumab 210mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg Q2W	83.6% (78.6-87.9)	67.3% (60.1-73.8)	41.1% (33.9-48.6)	15.4% (11.3-20.3)
Apremilast 20mg BID	*38.9% (29.5-49)*	*20.7% (14.2-28.9)*	*6.8% (4-11)*	*1.1% (0.6-2.2)*
Apremilast 30mg BID	49.4% (41.1-57.7)	29.2% (22.4-36.8)	11.1% (7.6-15.6)	2.2% (1.3-3.6)
Etanercept 50 mg / week	61.5% (54.1-68.6)	40.5% (33.3-48.1)	18% (13.5-23.6)	4.4% (2.9-6.5)
Etanercept 100 mg / week	*74% (68.8-78.8)*	*54.4% (48.2-60.5)*	*28.7% (23.7-34.3)*	*8.8% (6.5-11.5)*
Infliximab 5mg/kg	91.9% (87.9-94.9)	80.6% (73.8-86.6)	57.6% (48.6-66.8)	27.4% (20.3-35.9)
Ixekizumab 80mg Q4W	*95.2% (92.6-97)*	*87.1% (81.9-91.2)*	*67.7% (59.4-75.1)*	*36.9% (28.9-45.4)*
Ixekizumab 80mg Q2W	96.9% (95.1-98.1)	90.9% (86.9-93.8)	74.5% (67.4-80.7)	44.6% (36.6-52.9)
Secukinumab 150mg	*87.7% (83.1-91.3)*	*73.4% (66.4-79.6)*	*48.2% (40.2-56.1)*	*20% (14.9-26.1)*
Secukinumab 300mg	93.7% (90.9-95.8)	84% (78.9-88.3)	62.7% (55.2-69.8)	31.9% (25.4-39.1)
Ustekinumab 45mg	85.4% (79.6-90.1)	69.9% (61.6-77.4)	44% (35.3-53.2)	17.2% (12.1-23.8)
Ustekinumab 90mg	88.5% (82.5-92.9)	74.8% (65.6-82.6)	49.8% (39.3-60.4)	21.2% (14.3-29.8)
Ustekinumab (in-label dose)	86.1% (81.4-90)	71% (64.1-77.4)	45.3% (37.8-53.1)	18.1% (13.4-23.7)
DMF	38.4% (26.1-52.3)	20.4% (12-31.8)	6.7% (3.2-12.6)	1.1% (0.4-2.6)
Fumaderm	*44.8% (31.8-58.7)*	*25.3% (15.7-37.7)*	*9.1% (4.7-16.3)*	*1.7% (0.7-3.8)*
Methotrexate	*58.2% (47.3-68.1)*	*37.2% (27.3-47.5)*	*15.9% (10.1-23.2)*	*3.7% (1.9-6.3)*
Acitretin	*45% (25.9-65.1)*	*25.5% (11.9-44.2)*	*9.2% (3.2-20.7)*	*1.7% (0.4-5.4)*

Therapies other than the comparators of interest are shown in italics.
BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

b. Please provide pairwise comparisons of the relative risk (with 95% credible interval) of achieving a PASI ≥75 response for all interventions from sensitivity analysis 4.

Please see **Table *8***, which presents the relative risk (with 95% credible interval) of achieving a PASI ≥75 response for all pairwise comparisons from sensitivity analysis 4.

Table 8. Median risk ratio (95% credible interval) for all pairwise comparisons on PASI 75 response (sensitivity analysis 4)

BRO 140																			
[redacted]	BRO 210																		
[redacted]	[redacted]	ADA	0.31 (0.21, 0.42)	0.43 (0.34, 0.54)	0.6 (0.5, 0.71)	0.81 (0.72, 0.9)	1.2 (1.09, 1.33)	1.29 (1.18, 1.44)	1.35 (1.24, 1.5)	1.09 (0.98, 1.22)	1.25 (1.14, 1.38)	1.04 (0.92, 1.18)	1.11 (0.97, 1.26)	1.05 (0.95, 1.18)	0.3 (0.18, 0.47)	0.38 (0.24, 0.56)	0.55 (0.42, 0.69)	0.38 (0.18, 0.66)	0.09 (0.08, 0.11)
[redacted]	[redacted]	3.24 (2.35, 4.66)	APR 20	1.41 (1.04, 1.95)	1.95 (1.41, 2.8)	2.62 (1.92, 3.73)	3.88 (2.82, 5.63)	4.2 (3.04, 6.07)	4.38 (3.17, 6.34)	3.54 (2.57, 5.1)	4.05 (2.94, 5.85)	3.36 (2.44, 4.85)	3.59 (2.59, 5.21)	3.42 (2.48, 4.92)	0.98 (0.56, 1.68)	1.22 (0.72, 2.03)	1.79 (1.19, 2.69)	1.23 (0.56, 2.31)	0.3 (0.22, 0.42)
[redacted]	[redacted]	2.3 (1.85, 2.94)	0.71 (0.51, 0.96)	APR 30	1.38 (1.1, 1.78)	1.86 (1.52, 2.36)	2.75 (2.21, 3.56)	2.98 (2.39, 3.84)	3.11 (2.49, 4.01)	2.51 (2.02, 3.22)	2.87 (2.32, 3.7)	2.39 (1.91, 3.08)	2.55 (2.03, 3.31)	2.43 (1.95, 3.12)	0.7 (0.41, 1.12)	0.87 (0.54, 1.34)	1.27 (0.91, 1.74)	0.88 (0.41, 1.55)	0.21 (0.17, 0.27)
[redacted]	[redacted]	1.66 (1.4, 1.99)	0.51 (0.36, 0.71)	0.72 (0.56, 0.91)	ETA 50	1.34 (1.18, 1.55)	1.99 (1.69, 2.39)	2.15 (1.84, 2.56)	2.24 (1.91, 2.68)	1.81 (1.54, 2.16)	2.07 (1.77, 2.47)	1.72 (1.46, 2.06)	1.84 (1.55, 2.22)	1.75 (1.49, 2.09)	0.5 (0.3, 0.78)	0.63 (0.39, 0.94)	0.92 (0.67, 1.2)	0.63 (0.3, 1.08)	0.15 (0.13, 0.19)
[redacted]	[redacted]	1.24 (1.11, 1.38)	0.38 (0.27, 0.52)	0.54 (0.42, 0.66)	0.74 (0.64, 0.85)	ETA 100	1.48 (1.33, 1.66)	1.6 (1.47, 1.76)	1.67 (1.53, 1.84)	1.35 (1.22, 1.49)	1.54 (1.41, 1.7)	1.28 (1.15, 1.43)	1.37 (1.22, 1.53)	1.3 (1.18, 1.45)	0.38 (0.23, 0.58)	0.47 (0.29, 0.69)	0.69 (0.51, 0.86)	0.47 (0.22, 0.8)	0.12 (0.1, 0.14)
[redacted]	[redacted]	0.83 (0.75, 0.92)	0.26 (0.18, 0.36)	0.36 (0.28, 0.45)	0.5 (0.42, 0.59)	0.68 (0.6, 0.75)	INF	1.08 (1, 1.18)	1.13 (1.05, 1.22)	0.91 (0.82, 1.01)	1.04 (0.96, 1.13)	0.87 (0.76, 0.97)	0.93 (0.81, 1.04)	0.88 (0.79, 0.97)	0.25 (0.15, 0.39)	0.31 (0.2, 0.47)	0.46 (0.35, 0.57)	0.32 (0.15, 0.55)	0.08 (0.06, 0.1)
[redacted]	[redacted]	0.77 (0.7, 0.85)	0.24 (0.16, 0.33)	0.34 (0.26, 0.42)	0.47 (0.39, 0.54)	0.63 (0.57, 0.68)	0.93 (0.85, 1)	IXE Q4W	1.04 (1, 1.09)	0.84 (0.77, 0.91)	0.96 (0.91, 1.03)	0.8 (0.72, 0.89)	0.86 (0.76, 0.95)	0.82 (0.74, 0.89)	0.23 (0.14, 0.36)	0.29 (0.18, 0.43)	0.43 (0.32, 0.54)	0.29 (0.14, 0.5)	0.07 (0.06, 0.09)
[redacted]	[redacted]	0.74 (0.67, 0.81)	0.23 (0.16, 0.32)	0.32 (0.25, 0.4)	0.45 (0.37, 0.52)	0.6 (0.54, 0.65)	0.89 (0.82, 0.95)	0.96 (0.92, 1)	IXE Q2W	0.81 (0.74, 0.87)	0.93 (0.88, 0.97)	0.77 (0.69, 0.85)	0.82 (0.73, 0.91)	0.78 (0.72, 0.84)	0.22 (0.13, 0.35)	0.28 (0.17, 0.41)	0.41 (0.3, 0.52)	0.28 (0.13, 0.48)	0.07 (0.06, 0.09)
[redacted]	[redacted]	0.92 (0.82, 1.02)	0.28 (0.2, 0.39)	0.4 (0.31, 0.49)	0.55 (0.46, 0.65)	0.74 (0.67, 0.82)	1.1 (0.99, 1.22)	1.18 (1.09, 1.3)	1.24 (1.15, 1.35)	SEC 150	1.14 (1.08, 1.22)	0.95 (0.84, 1.07)	1.02 (0.9, 1.15)	0.97 (0.88, 1.06)	0.28 (0.17, 0.43)	0.35 (0.22, 0.51)	0.51 (0.38, 0.64)	0.35 (0.16, 0.6)	0.09 (0.07, 0.1)
[redacted]	[redacted]	0.8 (0.72, 0.88)	0.25 (0.17, 0.34)	0.35 (0.27, 0.43)	0.48 (0.4, 0.56)	0.65 (0.59, 0.71)	0.96 (0.88, 1.04)	1.04 (0.97, 1.1)	1.08 (1.03, 1.14)	0.87 (0.82, 0.92)	SEC 300	0.83 (0.74, 0.92)	0.89 (0.79, 0.98)	0.85 (0.78, 0.91)	0.24 (0.14, 0.38)	0.3 (0.19, 0.45)	0.44 (0.33, 0.56)	0.3 (0.14, 0.52)	0.07 (0.06, 0.09)
[redacted]	[redacted]	0.96 (0.85, 1.09)	0.3 (0.21, 0.41)	0.42 (0.32, 0.52)	0.58 (0.49, 0.69)	0.78 (0.7, 0.87)	1.15 (1.03, 1.31)	1.25 (1.13, 1.4)	1.3 (1.18, 1.46)	1.05 (0.94, 1.19)	1.2 (1.09, 1.35)	UST 45	1.07 (0.96, 1.18)	1.02 (0.9, 1.15)	0.29 (0.17, 0.45)	0.36 (0.23, 0.54)	0.53 (0.39, 0.68)	0.37 (0.17, 0.63)	0.09 (0.07, 0.11)
[redacted]	[redacted]	0.9 (0.79, 1.03)	0.28 (0.19, 0.39)	0.39 (0.3, 0.49)	0.54 (0.45, 0.65)	0.73 (0.65, 0.82)	1.08 (0.96, 1.23)	1.16 (1.05, 1.31)	1.21 (1.1, 1.37)	0.98 (0.87, 1.12)	1.12 (1.02, 1.27)	0.93 (0.84, 1.04)	UST 90	0.95 (0.84, 1.08)	0.27 (0.16, 0.43)	0.34 (0.21, 0.51)	0.5 (0.37, 0.64)	0.34 (0.16, 0.59)	0.08 (0.07, 0.1)
[redacted]	[redacted]	0.95 (0.85, 1.05)	0.29 (0.2, 0.4)	0.41 (0.32, 0.51)	0.57 (0.48, 0.67)	0.77 (0.69, 0.85)	1.13 (1.03, 1.26)	1.23 (1.13, 1.34)	1.28 (1.19, 1.4)	1.03 (0.94, 1.13)	1.18 (1.1, 1.28)	0.98 (0.87, 1.11)	1.05 (0.92, 1.19)	UST label	0.29 (0.17, 0.44)	0.36 (0.22, 0.53)	0.53 (0.39, 0.66)	0.36 (0.17, 0.62)	0.09 (0.07, 0.11)
[redacted]	[redacted]	3.29 (2.13, 5.49)	1.02 (0.59, 1.79)	1.43 (0.89, 2.42)	1.98 (1.27, 3.31)	2.66 (1.74, 4.42)	3.94 (2.55, 6.65)	4.26 (2.76, 7.16)	4.45 (2.87, 7.49)	3.59 (2.33, 6.01)	4.11 (2.67, 6.9)	3.42 (2.21, 5.73)	3.65 (2.35, 6.15)	3.47 (2.26, 5.81)	DMF	1.24 (0.86, 1.82)	1.82 (1.1, 3.14)	1.25 (0.54, 2.62)	0.31 (0.2, 0.5)
[redacted]	[redacted]	2.65 (1.79, 4.21)	0.82 (0.49, 1.39)	1.15 (0.75, 1.86)	1.6 (1.07, 2.54)	2.15 (1.46, 3.4)	3.18 (2.14, 5.09)	3.43 (2.32, 5.49)	3.58 (2.42, 5.74)	2.89 (1.96, 4.61)	3.31 (2.24, 5.29)	2.75 (1.85, 4.4)	2.94 (1.97, 4.72)	2.8 (1.9, 4.46)	0.81 (0.55, 1.17)	FUM	1.47 (0.92, 2.42)	1 (0.44, 2.04)	0.25 (0.17, 0.39)
[redacted]	[redacted]	1.8 (1.45, 2.37)	0.56 (0.37, 0.84)	0.79 (0.58, 1.1)	1.09 (0.83, 1.48)	1.46 (1.16, 1.95)	2.16 (1.76, 2.83)	2.33 (1.84, 3.15)	2.44 (1.92, 3.3)	1.97 (1.55, 2.66)	2.25 (1.78, 3.04)	1.87 (1.47, 2.54)	2 (1.56, 2.73)	1.9 (1.5, 2.57)	0.55 (0.32, 0.91)	0.81 (0.55, 1.17)	MTX	0.69 (0.32, 1.25)	0.17 (0.13, 0.22)
[redacted]	[redacted]	2.63 (1.52, 5.57)	0.81 (0.43, 1.79)	1.14 (0.65, 2.44)	1.58 (0.93, 3.3)	2.13 (1.25, 4.46)	3.15 (1.83, 6.72)	3.41 (1.98, 7.26)	3.55 (2.07, 7.58)	2.87 (1.67, 6.11)	3.29 (1.91, 6.99)	2.73 (1.59, 5.79)	2.92 (1.7, 6.2)	2.78 (1.61, 5.89)	0.8 (0.38, 1.85)	0.55 (0.32, 0.91)	1.46 (0.8, 3.14)	ACI	0.25 (0.14, 0.51)
[redacted]	[redacted]	10.73 (8.92, 13.03)	3.31 (2.37, 4.52)	4.66 (3.7, 5.81)	6.46 (5.37, 7.83)	8.69 (7.38, 10.31)	12.87 (10.5, 15.93)	13.91 (11.3, 17.29)	14.52 (11.73, 18.14)	11.72 (9.66, 14.36)	13.42 (10.96, 16.59)	11.14 (9.16, 13.71)	11.91 (9.69, 14.82)	11.34 (9.38, 13.83)	3.26 (1.99, 5.01)	4.05 (2.58, 5.99)	5.94 (4.45, 7.69)	4.07 (1.95, 7.08)	PBO

c. **Please provide the results of sensitivity analysis 4 in the form of CODA for use in the economic model.**

Please see data on tab "SA4" provided in separate SA_Coda_for_CEM.xls.

d. **Please provide clinical evidence to show the importance of the 30% threshold used in sensitivity analysis 4 for randomised patients who had previously tried biological therapy.**

The 30% threshold of prior exposure to biological therapy was chosen for pragmatic reasons, rather than a clear clinical rationale. A 20% threshold was used in the manufacturer submission for TA 350 (no rationale provided) and was considered for use in this submission; however, at this threshold, four of the five brodalumab studies would be excluded. Using a 30% threshold meant that only two of the brodalumab studies (AMAGINE-1 and Papp et al. 2012) were excluded.

Results of subgroup analyses reported in Appendix E of the submission indicate similar levels of relative efficacy in patients with and without prior biologic exposure. This is consistent with evidence presented in previous NICE STAs of other psoriasis treatments. This suggests that the NMA results are unlikely to vary substantially at different thresholds. Indeed, the results of sensitivity analysis 4 are not dissimilar to the results of the base case.

e. **Please clarify whether or not trials that did not report a % of patients having previously tried biological therapy were included in the NMA of sensitivity analysis 4.**

Studies that did not report a percentage of patients having previously tried biological therapy at baseline were included in sensitivity analysis 4. Most trials that did not specifically report a percentage of patients having previously tried biological therapy evaluated an anti-TNF therapy, were published before 2012 and specified that patients must be anti-TNF naïve at study entry. It was therefore assumed that the majority, if not all, of these patients were biologic therapy naïve.

A20. Priority Question: Please provide the predicted PASI 75, 90 and 100 responses for all interventions and the associated CODA for use in the economic model for:

a. **The NMA that excludes all phase II studies.**

Table 9 presents the absolute predicted PASI 50, 75, 90 and 100 responses (with 95% credible intervals) for all interventions from a sensitivity analysis in which all phase II studies (Nakagawa *et al.* 2016; Papp *et al.* 2012; X-PLORE; PSOR-005; Papp *et al.* 2013; Ohtsuki *et al.* 2017; Gottlieb *et al.* 2003; Gordon *et al.* 2006; Chaudhari *et al.* 2001;

SPIRIT) were removed. Note that upon removing these studies, there is no longer any data for apremilast 20 mg twice daily, therefore it does not appear in the table.

For the associated CODA, please see data on tab “SA_excluding_ph2” provided in separate SA_Coda_for_CEM.xls.

Table 9 : Predicted PASI responses for evaluated interventions – Sensitivity analysis excluding all phase II studies

Treatment	Probability of PASI response, median (95% CrI)			
	PASI 50	PASI 75	PASI 90	PASI 100
Placebo	13.9% (11.5-16.6)	5.4% (4.3-6.8)	1.2% (0.8-1.6)	0.1% (0.1-0.2)
Brodalumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]
Brodalumab 210mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg Q2W	81.4% (75.8-86)	64.5% (57.1-71.2)	38.4% (31.3-45.8)	13.8% (10-18.4)
Apremilast 30mg BID	45.8% (37.2-54.5)	26.6% (19.9-34.2)	9.8% (6.5-14.2)	1.8% (1-3.1)
Etanercept 50 mg / week	57.8% (50.2-65.2)	37.3% (30.3-44.9)	16.1% (11.9-21.4)	3.7% (2.4-5.6)
Etanercept 100 mg / week	71.5% (66.2-76.4)	51.9% (46-57.9)	26.9% (22.1-32.1)	7.9% (5.9-10.4)
Infliximab 5mg/kg	90.7% (86.3-94.1)	78.9% (71.6-85.1)	55.4% (46.2-64.6)	25.5% (18.6-33.7)
Ixekizumab 80mg Q4W	94.5% (92-96.4)	86% (81.3-89.9)	66.1% (58.8-72.9)	35.2% (28.3-42.6)
Ixekizumab 80mg Q2W	96.3% (94.5-97.6)	89.7% (86-92.7)	72.6% (66.1-78.5)	42.2% (35.1-49.7)
Secukinumab 150mg	86% (81.2-89.9)	71.3% (64.3-77.6)	45.9% (38.3-53.7)	18.4% (13.7-24.1)
Secukinumab 300mg	92.9% (90-95.1)	82.8% (77.6-87.2)	61% (53.8-68)	30.3% (24.1-37.1)
Ustekinumab 45mg	85.4% (80.8-89.2)	70.4% (63.7-76.4)	44.8% (37.6-52.2)	17.7% (13.3-22.9)
Ustekinumab 90mg	87.9% (83.6-91.4)	74.3% (67.6-80.2)	49.4% (41.7-57.2)	20.9% (15.7-26.9)
Ustekinumab (in-label dose)	84.8% (79.9-88.9)	69.4% (62.5-75.8)	43.7% (36.4-51.3)	17% (12.6-22.3)
DMF	35.6% (23.6-49.2)	18.7% (10.7-29.5)	6% (2.8-11.4)	0.9% (0.3-2.3)
Fumaderm	41.8% (28.8-55.6)	23.3% (14-35.2)	8.2% (4-14.8)	1.4% (0.5-3.3)
Methotrexate	55.1% (44-65.2)	34.7% (25.1-44.9)	14.5% (9.1-21.3)	3.2% (1.6-5.6)
Acitretin	42.1% (23.5-62.4)	23.6% (10.7-41.9)	8.3% (2.8-19.2)	1.5% (0.3-4.8)

Therapies other than the comparators of interest are shown in italics.
BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

b. The NMA that excludes the two brodalumab phase II trials, i.e., excluding Nakagawa et al., (2016) and Papp et al., (2012).

Table 10 presents the absolute predicted PASI 50, 75, 90 and 100 responses (with 95% credible intervals) for all interventions from a sensitivity analysis in which the two brodalumab phase II studies (Nakagawa *et al.* 2016; Papp *et al.* 2012) were removed.

For the associated CODA, please see data on tab “SA_excluding_BROph2” provided in separate SA_Coda_for_CEM.xls.

Table 10 : Predicted PASI responses for evaluated interventions – Sensitivity analysis excluding Papp *et al.* 2012 and Nakagawa *et al.* 2016

Treatment	Probability of PASI response, median (95% CrI)			
	PASI 50	PASI 75	PASI 90	PASI 100
Placebo	14.7% (12.4-17.3)	5.7% (4.6-7.1)	1.2% (0.9-1.6)	0.1% (0.1-0.2)
Brodalumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]
Brodalumab 210mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg Q2W	82.6% (77.7-86.7)	65.9% (59.2-72.1)	39.9% (33.2-46.8)	14.7% (11-19.1)
Apremilast 20mg BID	36.9% (27.9-46.4)	19.4% (13.3-26.8)	6.3% (3.8-10)	1% (0.5-1.9)
Apremilast 30mg BID	46.8% (39.5-54.2)	27.2% (21.4-33.6)	10.2% (7.2-13.8)	1.9% (1.2-3)
Etanercept 50 mg / week	59.9% (52.8-66.7)	39.1% (32.4-46.2)	17.3% (13.1-22.3)	4.1% (2.7-6)
Etanercept 100 mg / week	73% (68.1-77.4)	53.4% (47.7-58.9)	28% (23.5-33)	8.4% (6.4-10.9)
Infliximab 5mg/kg	90.9% (86.9-94)	79.1% (72.4-84.8)	55.7% (47.2-64.1)	25.8% (19.3-33.2)
Ixekizumab 80mg Q4W	95% (92.8-96.6)	86.8% (82.4-90.3)	67.4% (60.5-73.7)	36.6% (29.8-43.6)
Ixekizumab 80mg Q2W	96.6% (95.1-97.8)	90.4% (86.9-93)	73.8% (67.7-79.2)	43.7% (36.8-50.7)
Secukinumab 150mg	87% (82.6-90.5)	72.5% (66-78.4)	47.3% (39.9-54.7)	19.4% (14.7-25)
Secukinumab 300mg	93.4% (90.8-95.4)	83.6% (78.8-87.7)	62.2% (55.3-68.9)	31.5% (25.5-38.1)
Ustekinumab 45mg	86.4% (82.2-89.8)	71.6% (65.3-77.2)	46.2% (39.3-53.1)	18.7% (14.3-23.7)
Ustekinumab 90mg	88.7% (84.8-91.9)	75.3% (69.1-80.8)	50.7% (43.3-58.1)	21.9% (16.8-27.8)
Ustekinumab (in-label dose)	85.7% (81.2-89.3)	70.5% (64-76.4)	44.9% (37.9-52.1)	17.8% (13.5-22.9)
DMF	36.8% (25-50.3)	19.4% (11.4-30.2)	6.3% (3.1-11.8)	1% (0.4-2.4)
Fumaderm	43.1% (30.5-56.9)	24.2% (15-36.1)	8.6% (4.4-15.4)	1.5% (0.6-3.5)
Methotrexate	56.3% (45.7-66)	35.6% (26.2-45.4)	15% (9.6-21.7)	3.4% (1.8-5.8)
Acitretin	43.7% (25.2-64.2)	24.6% (11.6-43.5)	8.8% (3.1-20.4)	1.6% (0.4-5.2)

Therapies other than the comparators of interest are shown in italics.
BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

A21. Priority Question: Please provide additional results from the placebo adjusted model:

a. Please provide the absolute predicted PASI 75, 90 and 100 responses (with 95% credible interval) for all interventions, i.e., the equivalent of Table 26 for the placebo adjusted model.

Please see **Table *11*** for the absolute predicted PASI 75, 90 and 100 responses (with 95% credible intervals) for all interventions from the placebo adjusted model.

Table 11: Predicted PASI responses for evaluated interventions – Placebo adjusted model 4

Treatment	Probability of PASI response, median (95% CrI)			
	PASI 50	PASI 75	PASI 90	PASI 100
Placebo	14.7% (12.5-17.2)	5.7% (4.6-7)	1.3% (1-1.6)	0.1% (0.1-0.2)
Brodalumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]
Brodalumab 210mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg Q2W	85% (82.3-87.3)	69.4% (65.5-73)	43.9% (39.6-48)	17.2% (14.5-20)
Apremilast 20mg BID	*43.8% (36.4-51.3)*	*24.7% (19.1-31.1)*	*8.9% (6.2-12.4)*	*1.6% (1-2.6)*
Apremilast 30mg BID	51.9% (46.7-56.8)	31.5% (27-36.1)	12.6% (10.1-15.4)	2.6% (1.9-3.5)
Etanercept 50 mg / week	59.8% (55-64.5)	39% (34.3-43.9)	17.3% (14.3-20.7)	4.1% (3.1-5.4)
Etanercept 100 mg / week	*71.2% (68.5-73.9)*	*51.3% (48.2-54.5)*	*26.4% (23.9-29.1)*	*7.7% (6.6-9)*
Infliximab 5mg/kg	90.9% (88.5-92.8)	78.9% (75-82.4)	55.6% (50.4-60.6)	25.7% (21.7-30.1)
Ixekizumab 80mg Q4W	*94.1% (92.5-95.5)*	*85.1% (81.9-87.9)*	*64.6% (59.8-69.4)*	*33.8% (29.3-38.7)*
Ixekizumab 80mg Q2W	96.1% (94.9-97)	89.1% (86.6-91.2)	71.5% (67.2-75.5)	41.1% (36.4-45.9)
Secukinumab 150mg	*85.2% (82.1-88.1)*	*69.8% (65.2-74.2)*	*44.2% (39.2-49.4)*	*17.4% (14.3-21)*
Secukinumab 300mg	92.5% (90.6-94.1)	81.8% (78.5-84.9)	59.7% (55.1-64.4)	29.2% (25.3-33.6)
Ustekinumab 45mg	85.2% (82.3-87.8)	69.7% (65.5-73.7)	44.2% (39.6-48.8)	17.4% (14.6-20.6)
Ustekinumab 90mg	87% (83.9-89.6)	72.5% (67.8-76.8)	47.4% (42.1-52.7)	19.5% (16.1-23.5)
Ustekinumab (in-label dose)	85.7% (82.7-88.5)	70.5% (66-74.9)	45.1% (40.2-50.3)	18% (14.8-21.7)
DMF	50.3% (40-60.5)	30.1% (21.7-39.6)	11.8% (7.4-17.7)	2.4% (1.3-4.3)
Fumaderm	*56.8% (46.6-66.6)*	*36% (27-46)*	*15.4% (10.1-22.3)*	*3.5% (1.9-6)*
Methotrexate	*58.4% (50.4-65.8)*	*37.6% (30.2-45.2)*	*16.4% (11.8-21.7)*	*3.8% (2.4-5.8)*
Acitretin	*42.7% (24.6-62.6)*	*23.8% (11.2-41.8)*	*8.5% (3-19.2)*	*1.5% (0.4-4.8)*

Therapies other than the comparators of interest are shown in italics.

BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

b. Please provide the relative risk at each PASI response (with 95% credible interval) for all interventions versus placebo, i.e., the equivalent of Table 27 for the placebo adjusted model.

Please see **Table *12*** for relative risk at each PASI response (with 95% credible interval) for all interventions versus placebo from the placebo adjusted model.

Table 12: Treatment effects at each level of PASI response for interventions versus placebo – placebo adjusted model

Treatment	Risk ratio versus placebo, median (95% Credible Interval)			
	PASI 50	PASI 75	PASI 90	PASI 100
Brodalumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]
Brodalumab 210mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg Q2W	5.77 (4.97 to 6.76)	12.08 (9.95 to 14.78)	34.86 (27.06 to 45.28)	141.1 (101.7 to 198.3)
Apremilast 20mg BID	*2.97 (2.4 to 3.67)*	*4.3 (3.21 to 5.71)*	*7.08 (4.75 to 10.45)*	*13.32 (7.8 to 22.56)*
Apremilast 30mg BID	3.52 (2.99 to 4.16)	5.47 (4.41 to 6.84)	10.02 (7.5 to 13.48)	21.65 (14.72 to 32.01)
Etanercept 50 mg / week	4.06 (3.47 to 4.77)	6.78 (5.5 to 8.39)	13.75 (10.38 to 18.26)	33.99 (23.41 to 49.39)
Etanercept 100 mg / week	*4.84 (4.18 to 5.63)*	*8.92 (7.4 to 10.83)*	*21.01 (16.49 to 26.95)*	*63.66 (46.52 to 87.34)*
Infliximab 5mg/kg	6.17 (5.3 to 7.24)	13.73 (11.27 to 16.86)	44.21 (34.08 to 57.72)	211.5 (150.2 to 300)
Ixekizumab 80mg Q4W	*6.39 (5.49 to 7.52)*	*14.8 (12.13 to 18.21)*	*51.45 (39.71 to 67.13)*	*278.6 (198.3 to 393.9)*
Ixekizumab 80mg Q2W	6.52 (5.6 to 7.67)	15.5 (12.69 to 19.09)	56.84 (43.87 to 74.29)	337.9 (242 to 477)
Secukinumab 150mg	*5.79 (4.98 to 6.79)*	*12.14 (9.96 to 14.91)*	*35.2 (27.06 to 46.07)*	*143.4 (101 to 204.5)*
Secukinumab 300mg	6.28 (5.39 to 7.38)	14.24 (11.7 to 17.51)	47.54 (36.72 to 62.01)	240.9 (172 to 339.3)
Ustekinumab 45mg	5.78 (4.97 to 6.77)	12.13 (9.97 to 14.88)	35.14 (27.18 to 45.78)	143.1 (102 to 201.7)
Ustekinumab 90mg	5.9 (5.07 to 6.93)	12.61 (10.33 to 15.5)	37.68 (28.9 to 49.32)	160.8 (112.8 to 229.5)
Ustekinumab (in-label dose)	5.82 (5 to 6.83)	12.27 (10.07 to 15.1)	35.88 (27.62 to 47.01)	148.3 (104.7 to 211.5)
Dimethyl Fumarate	3.41 (2.64 to 4.31)	5.23 (3.67 to 7.28)	9.39 (5.72 to 14.97)	19.77 (10.03 to 37.67)
Fumaderm	*3.85 (3.06 to 4.78)*	*6.26 (4.52 to 8.5)*	*12.21 (7.71 to 18.88)*	*28.67 (15.19 to 52.78)*
Methotrexate	*3.96 (3.27 to 4.79)*	*6.53 (5 to 8.47)*	*13.01 (8.94 to 18.64)*	*31.43 (18.75 to 51.46)*
Acitretin	*2.9 (1.66 to 4.35)*	*4.14 (1.93 to 7.44)*	*6.73 (2.37 to 15.61)*	*12.43 (3.07 to 40.49)*

Therapies other than the comparators of interest are shown in italics.
BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

c. Please provide the relative risk at each PASI response (with 95% credible interval) for brodalumab 210 mg versus comparator interventions, i.e., the equivalent of Table 28 for the placebo adjusted model.

Please see **Table *13*** for relative risk at each PASI response (with 95% credible interval) for brodalumab 210 mg versus comparator interventions from the placebo adjusted model.

Table 13: Treatment effects at each level of PASI response for brodalumab 210 mg vs comparators – placebo adjusted model

Treatment	Risk ratio brodalumab 210 mg versus comparator, median (95% CrI)			
	PASI 50	PASI 75	PASI 90	PASI 100
Brodalumab 140mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast 20mg BID	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast 30mg BID	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 50 mg / week	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept 100 mg / week	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab 5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80mg Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab 80mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300mg	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 45mg	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 90mg	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab (in-label dose)	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl Fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Fumaderm	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]
Acitretin	[redacted]	[redacted]	[redacted]	[redacted]

Therapies other than the comparators of interest are shown in italics.
Risk ratios in bold indicate statistically significant differences.
BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

d. Please provide pairwise comparisons of the relative risk (with 95% credible interval) of achieving a PASI ≥75 response for all interventions.

Please see **Table *14***, which presents the relative risk (with 95% credible interval) of achieving a PASI ≥75 response for all pairwise comparisons from the placebo adjusted analysis.

Table 14. Median risk ratio (95% credible interval) for all pairwise comparisons on PASI 75 response (placebo adjusted analysis)

BRO 140	BRO 210																		
[redacted]	[redacted]	ADA	0.36 (0.28, 0.45)	0.45 (0.39, 0.52)	0.56 (0.49, 0.64)	0.74 (0.68, 0.8)	1.14 (1.06, 1.22)	1.22 (1.15, 1.31)	1.28 (1.21, 1.36)	1.01 (0.92, 1.09)	1.18 (1.11, 1.26)	1 (0.93, 1.08)	1.04 (0.96, 1.13)	1.02 (0.94, 1.1)	0.43 (0.31, 0.57)	0.52 (0.39, 0.66)	0.54 (0.44, 0.65)	0.34 (0.16, 0.6)	0.08 (0.07, 0.1)
[redacted]	[redacted]	2.81 (2.23, 3.63)	APR 20	1.27 (1, 1.65)	1.58 (1.22, 2.08)	2.08 (1.64, 2.69)	3.19 (2.53, 4.14)	3.44 (2.73, 4.47)	3.6 (2.86, 4.67)	2.82 (2.23, 3.67)	3.31 (2.63, 4.29)	2.82 (2.23, 3.66)	2.93 (2.31, 3.82)	2.85 (2.26, 3.71)	1.22 (0.84, 1.74)	1.46 (1.04, 2.04)	1.52 (1.12, 2.06)	0.97 (0.44, 1.78)	0.23 (0.18, 0.31)
[redacted]	[redacted]	2.2 (1.91, 2.56)	0.79 (0.6, 1)	APR 30	1.24 (1.04, 1.48)	1.63 (1.41, 1.91)	2.5 (2.17, 2.93)	2.7 (2.34, 3.15)	2.83 (2.46, 3.29)	2.21 (1.9, 2.6)	2.6 (2.26, 3.03)	2.21 (1.91, 2.59)	2.3 (1.98, 2.7)	2.24 (1.94, 2.63)	0.96 (0.69, 1.29)	1.14 (0.85, 1.5)	1.19 (0.93, 1.5)	0.76 (0.35, 1.35)	0.18 (0.15, 0.23)
[redacted]	[redacted]	1.78 (1.57, 2.03)	0.63 (0.48, 0.82)	0.81 (0.67, 0.96)	ETA 50	1.32 (1.17, 1.49)	2.02 (1.79, 2.31)	2.18 (1.94, 2.48)	2.29 (2.03, 2.59)	1.79 (1.57, 2.05)	2.1 (1.86, 2.39)	1.79 (1.58, 2.04)	1.86 (1.64, 2.13)	1.81 (1.59, 2.07)	0.77 (0.55, 1.04)	0.92 (0.68, 1.22)	0.97 (0.75, 1.2)	0.61 (0.29, 1.07)	0.15 (0.12, 0.18)
[redacted]	[redacted]	1.35 (1.25, 1.46)	0.48 (0.37, 0.61)	0.61 (0.52, 0.71)	0.76 (0.67, 0.85)	ETA 100	1.54 (1.43, 1.65)	1.66 (1.56, 1.76)	1.74 (1.64, 1.84)	1.36 (1.26, 1.47)	1.6 (1.5, 1.7)	1.36 (1.26, 1.46)	1.41 (1.31, 1.52)	1.38 (1.27, 1.49)	0.59 (0.42, 0.78)	0.7 (0.52, 0.9)	0.73 (0.59, 0.89)	0.46 (0.22, 0.81)	0.11 (0.09, 0.14)
[redacted]	[redacted]	0.88 (0.82, 0.94)	0.31 (0.24, 0.4)	0.4 (0.34, 0.46)	0.49 (0.43, 0.56)	0.65 (0.61, 0.7)	INF	1.08 (1.02, 1.14)	1.13 (1.07, 1.19)	0.88 (0.82, 0.95)	1.04 (0.98, 1.1)	0.88 (0.82, 0.95)	0.92 (0.85, 0.99)	0.89 (0.83, 0.97)	0.38 (0.28, 0.5)	0.46 (0.34, 0.59)	0.48 (0.39, 0.57)	0.3 (0.14, 0.53)	0.07 (0.06, 0.09)
[redacted]	[redacted]	0.82 (0.76, 0.87)	0.29 (0.22, 0.37)	0.37 (0.32, 0.43)	0.46 (0.4, 0.52)	0.6 (0.57, 0.64)	0.93 (0.87, 0.98)	IXE Q4W	1.05 (1.01, 1.08)	0.82 (0.76, 0.88)	0.96 (0.92, 1.01)	0.82 (0.77, 0.87)	0.85 (0.79, 0.91)	0.83 (0.77, 0.89)	0.35 (0.25, 0.47)	0.42 (0.32, 0.54)	0.44 (0.35, 0.53)	0.28 (0.13, 0.49)	0.07 (0.05, 0.08)
[redacted]	[redacted]	0.78 (0.73, 0.82)	0.28 (0.21, 0.35)	0.35 (0.3, 0.41)	0.44 (0.39, 0.49)	0.58 (0.54, 0.61)	0.89 (0.84, 0.93)	0.96 (0.92, 0.99)	IXE Q2W	0.78 (0.73, 0.83)	0.92 (0.88, 0.96)	0.78 (0.73, 0.83)	0.81 (0.76, 0.86)	0.79 (0.74, 0.84)	0.34 (0.24, 0.45)	0.4 (0.3, 0.52)	0.42 (0.34, 0.51)	0.27 (0.13, 0.47)	0.06 (0.05, 0.08)
[redacted]	[redacted]	0.99 (0.92, 1.08)	0.35 (0.27, 0.45)	0.45 (0.38, 0.52)	0.56 (0.49, 0.64)	0.73 (0.68, 0.8)	1.13 (1.05, 1.22)	1.22 (1.14, 1.31)	1.28 (1.2, 1.37)	SEC 150	1.17 (1.11, 1.24)	1 (0.92, 1.08)	1.04 (0.95, 1.13)	1.01 (0.93, 1.1)	0.43 (0.31, 0.57)	0.52 (0.38, 0.67)	0.54 (0.43, 0.66)	0.34 (0.16, 0.6)	0.08 (0.07, 0.1)
[redacted]	[redacted]	0.85 (0.79, 0.9)	0.3 (0.23, 0.38)	0.39 (0.33, 0.44)	0.48 (0.42, 0.54)	0.63 (0.59, 0.67)	0.96 (0.91, 1.02)	1.04 (0.99, 1.09)	1.09 (1.04, 1.14)	0.85 (0.8, 0.9)	SEC 300	0.85 (0.8, 0.91)	0.89 (0.82, 0.95)	0.86 (0.81, 0.92)	0.37 (0.26, 0.49)	0.44 (0.33, 0.56)	0.46 (0.37, 0.55)	0.29 (0.14, 0.51)	0.07 (0.06, 0.09)
[redacted]	[redacted]	1 (0.92, 1.08)	0.35 (0.27, 0.45)	0.45 (0.39, 0.52)	0.56 (0.49, 0.63)	0.74 (0.68, 0.79)	1.13 (1.05, 1.22)	1.22 (1.15, 1.3)	1.28 (1.2, 1.36)	1 (0.92, 1.09)	1.17 (1.1, 1.26)	UST 45	1.04 (0.98, 1.11)	1.01 (0.93, 1.1)	0.43 (0.31, 0.57)	0.52 (0.38, 0.67)	0.54 (0.43, 0.65)	0.34 (0.16, 0.6)	0.08 (0.07, 0.1)
[redacted]	[redacted]	0.96 (0.88, 1.04)	0.34 (0.26, 0.43)	0.43 (0.37, 0.51)	0.54 (0.47, 0.61)	0.71 (0.66, 0.76)	1.09 (1.01, 1.17)	1.17 (1.1, 1.26)	1.23 (1.16, 1.31)	0.96 (0.89, 1.05)	1.13 (1.06, 1.21)	0.96 (0.9, 1.03)	UST 90	0.97 (0.9, 1.06)	0.42 (0.3, 0.55)	0.5 (0.37, 0.64)	0.52 (0.41, 0.63)	0.33 (0.16, 0.58)	0.08 (0.06, 0.1)
[redacted]	[redacted]	0.98 (0.91, 1.07)	0.35 (0.27, 0.44)	0.45 (0.38, 0.52)	0.55 (0.48, 0.63)	0.73 (0.67, 0.79)	1.12 (1.04, 1.21)	1.21 (1.13, 1.29)	1.26 (1.19, 1.35)	0.99 (0.91, 1.07)	1.16 (1.09, 1.24)	0.99 (0.91, 1.07)	1.03 (0.94, 1.12)	UST label	0.43 (0.31, 0.56)	0.51 (0.38, 0.66)	0.53 (0.43, 0.65)	0.34 (0.16, 0.6)	0.08 (0.07, 0.1)
[redacted]	[redacted]	2.3 (1.76, 3.18)	0.82 (0.57, 1.19)	1.05 (0.78, 1.46)	1.29 (0.96, 1.82)	1.7 (1.28, 2.37)	2.62 (1.98, 3.64)	2.82 (2.14, 3.92)	2.95 (2.24, 4.11)	2.31 (1.74, 3.23)	2.71 (2.06, 3.78)	2.31 (1.74, 3.23)	2.4 (1.81, 3.35)	2.34 (1.77, 3.25)	DMF	1.2 (0.9, 1.61)	1.25 (0.88, 1.79)	0.79 (0.35, 1.51)	0.19 (0.14, 0.27)
[redacted]	[redacted]	1.93 (1.51, 2.56)	0.69 (0.49, 0.96)	0.87 (0.67, 1.18)	1.08 (0.82, 1.47)	1.42 (1.11, 1.91)	2.19 (1.7, 2.93)	2.36 (1.84, 3.16)	2.47 (1.93, 3.31)	1.94 (1.5, 2.61)	2.27 (1.77, 3.05)	1.93 (1.5, 2.6)	2.01 (1.55, 2.71)	1.96 (1.52, 2.63)	0.84 (0.62, 1.11)	FUM	1.04 (0.76, 1.46)	0.66 (0.3, 1.24)	0.16 (0.12, 0.22)
[redacted]	[redacted]	1.84 (1.54, 2.29)	0.66 (0.48, 0.89)	0.84 (0.67, 1.07)	1.04 (0.83, 1.33)	1.36 (1.13, 1.71)	2.1 (1.76, 2.58)	2.26 (1.87, 2.82)	2.37 (1.97, 2.95)	1.85 (1.53, 2.33)	2.17 (1.8, 2.72)	1.85 (1.53, 2.32)	1.93 (1.59, 2.42)	1.87 (1.55, 2.35)	0.8 (0.56, 1.13)	0.84 (0.62, 1.11)	MTX	0.64 (0.29, 1.15)	0.15 (0.12, 0.2)
[redacted]	[redacted]	2.91 (1.66, 6.2)	1.04 (0.56, 2.27)	1.32 (0.74, 2.84)	1.63 (0.93, 3.45)	2.15 (1.23, 4.56)	3.31 (1.89, 7.05)	3.57 (2.04, 7.58)	3.74 (2.13, 7.92)	2.93 (1.67, 6.24)	3.43 (1.96, 7.28)	2.93 (1.67, 6.2)	3.04 (1.73, 6.44)	2.96 (1.68, 6.31)	1.26 (0.66, 2.83)	0.8 (0.56, 1.13)	1.57 (0.87, 3.41)	ACI	0.24 (0.13, 0.52)
[redacted]	[redacted]	12.08 (9.95, 14.78)	4.3 (3.21, 5.71)	5.47 (4.41, 6.84)	6.78 (5.5, 8.39)	8.92 (7.4, 10.84)	13.73 (11.27, 16.86)	14.8 (12.13, 18.21)	15.5 (12.69, 19.09)	12.14 (9.96, 14.91)	14.24 (11.7, 17.51)	12.13 (9.97, 14.88)	12.61 (10.33, 15.5)	12.27 (10.07, 15.1)	5.23 (3.67, 7.28)	6.26 (4.52, 8.5)	6.53 (5, 8.47)	4.14 (1.93, 7.44)	PBO

e. Please provide the programming WinBUGS code for the placebo adjusted model.

Index

1 = Placebo
2 = Brodalumab (140 mg)
3 = Brodalumab (210 mg)
4 = Adalimumab (40 mg)
5 = Apremilast (20 mg)
6 = Apremilast (30 mg)
7 = Etanercept (50 mg/week)
8 = Etanercept (100 mg/week)
9 = Infliximab (5 mg/kg)
10 = Ixekizumab (80 mg Q4W)
11 = Ixekizumab (80 mg Q2W)
12 = Secukinumab (150 mg)
13 = Secukinumab (300 mg)
14 = Ustekinumab (45 mg)
15 = Ustekinumab (90 mg)
16 = Ustekinumab (in-label dose)
17 = Dimethyl Fumarate
18 = Fumaderm
19 = Methotrexate
20 = Acitretin

Model

Each trial reported the number of patients in mutually exclusive categories, representing the percentage improvement in symptoms. These categories define 5 cut-off points of % improvement, as follows
C=1: 0
C=2: 50
C=3: 75
C=4: 90
C=5: 100
Data are transformed to conditional binomials.

```
# Binomial likelihood, probit link (different categories)
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 #   LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0            # treatment effect is zero for control arm
# vague priors for all trial baselines
   mu[i] ~ dnorm(0,.01)

 for (k in 1:na[i]) {           # LOOP THROUGH ARMS
     p[i,k,1] <- 1              # Pr(PASI >0)
    for (j in 1:nc[i]-1) {      # LOOP THROUGH CATEGORIES

# binomial likelihood
          r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j])
# conditional probabilities
          q[i,k,j] <- 1-(p[i,k,C[i,j+1]]/p[i,k,C[i,j]])
           theta[i,k,j] <- mu[i] + delta[i,k] - delta[i,1] + (bcov[t[i,k]] - bcov[t[i,1]]) * (mu[i]-mx) + z[C[i,j+1]-1] # linear predictor
          rhat[i,k,j] <-  q[i,k,j] * n[i,k,j]  # predicted number events

#Deviance contribution of each category
          dv[i,k,j] <- 2 * (r[i,k,j]*(log(r[i,k,j])-log(rhat[i,k,j]))
   +(n[i,k,j]-r[i,k,j])*(log(n[i,k,j]-r[i,k,j]) - log(n[i,k,j]-rhat[i,k,j])))
        }
```

```
      dev[i,k] <- sum(dv[i,k,1:nc[i]-1]) # deviance contribution of each arm
      for (j in 2:nc[i])  {  # LOOP THROUGH CATEGORIES

         p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j]   # link function
# adjust link function phi(x) for extreme values that can give numerical errors
# when x< -5, phi(x)=0, when x> 5, phi(x)=1
         phi.adj[i,k,j] <- step(5+theta[i,k,j-1])
              * (step(theta[i,k,j-1]-5)
                + step(5-theta[i,k,j-1])*phi(theta[i,k,j-1]) )
        }
     }
   for (k in 2:na[i]) {        # LOOP THROUGH ARMS
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LHR distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LHR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
     }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
 }
z[1] <- 0                    # set z50=0
#Set priors for z, for any number of categories
for (j in 2:Cmax-1)  {
        z.aux[j] ~ dunif(0,2)                  #priors
       z[j] <- z[j-1] + z.aux[j]               #ensures z[j]~Uniform(z[j-1],z[j-1]+5
                  }

totresdev <- sum(resdev[])    #Total Residual Deviance
for (k in 2:nt){
d[k] ~ dnorm(0,0.01)  # vague priors for treatment effects
bcov[k] <- B
}
B ~ dnorm(0,0.01)

d[1] <- 0      # treatment effect is zero for reference treatment

bcov[1] <- 0#covariate effect is zero for placebo

mx <- mean(mu[])

sd ~ dunif(0,2)               # vague prior for between-trial SD
tau <- pow(sd,-2)     # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural
# (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
#
A ~ dnorm(meanA,precA)
for (k in 1:nt) {
# calculate prob of achieving PASI 50,75,90,100 on treat k
   for (j in 1:Cmax-1) {  T[j,k] <- 1 - phi(A + d[k] + z[j] + (bcov[k]-bcov[1]) * (A-mx))}
 }
for(k in 2:nt) {
#calculate relative risk for each PASI response
for(j in 1:4) {rr[j,k] <- T[j,k]/T[j,1]}
             for (j in 1:4) {rrBROhigh[j,k] <- T[j,3]/T[j,k]}

for (j in 1:4) { or[j,k] <- (T[j,k]/(1-T[j,k]))/(T[j,1]/(1-T[j,1]))}
```

```
        for (j in 1:4) { orBROhigh[j,k] <- (T[j,3]/(1-T[j,3]))/(T[j,k]/(1-T[j,k]))}
            }
}                       # *** PROGRAM ENDS
```

Data

[redacted]

[redacted]

[redacted]

[redacted]

END

Initial Values

#chain 1

```
list(d = c(NA,1,1,0,1,  0,1,0,1,0,  0,1,0,1,0,  0,1,0,1,0), A=1, B=0,
mu = c(0,0,0,0,0,0,  0,0,0,0,0,0,  0,0,0,0,0,0,  0,0,0,0,0,0,  0,0,0,0,0,0,  0,0,0,0,0,0,  0,0,0,0,0,0,  0,0,0,0,0,0,  0,0,0,0,0,0,
0,0,0,0,0,0,  0,0,0,0),  sd=0.3,  z.aux=c(NA, 0.5,NA, NA))


#chain 2
list(d = c(NA,1,0,0,1, 0,0,0,1,0, 0,0, 0,0,0,  1,0,0,0,0), A=0.5, B=0.2,
mu = c(1,0,0,1,0,  1,0,0,1,0,  1,0,0,1,0,  1,0,0,1,0,  1,0,0,1,0,  1,0,0,1,0,  1,0,0,1,0,  1,0,0,1,0,  1,0,0,1,0,  1,0,0,1,0,  1,0,0,1,0,
1,0,0,1),  sd = 0.5,  z.aux=c(NA, 0.3,NA, NA))

#chain 3
list(d = c(NA,-1,0,-1,1,  1,-1,0,-1,1,  1,-1,0,-1,1,  1,-1,0,-1,1,  1,-1,0,-1,1), A=1.1, B=-0.1
mu = c(1,1,1,1,1,1,  1,1,1,1,1,1,  1,1,1,1,1,1,  1,1,1,1,1,1,  1,1,1,1,1,1,  1,1,1,1,1,1,  1,1,1,1,1,1,  1,1,1,1,1,1,  1,1,1,1,1,1,  1,1,1,1,1,
1,1,1,1),  sd = 0.3,  z.aux=c(NA, 0.2,NA, NA))
```

A22. The WinBUGS code uses <u>'meanA = 1.048518029' and 'precA = 367.0025436'</u> for the baseline placebo effect. Please provide an explanation for how these quantities were estimated. Please provide details of any evidence used to support this estimation.

Baseline risk of PASI response was estimated using methods described by Dias and colleagues[4]. PASI 50 response outcomes for placebo from included studies were used to inform the baseline event rates and estimated through separate Bayesian analysis in WinBUGS. The natural history model provides an estimates of baseline risk based on the posterior mean and standard deviation of the observed data. A probability of achieving PASI 50 with placebo was estimated for each analysis and translated onto the probit scale, by finding the inverse of the normal cumulative distribution.

Table *15* presents the studies which reported PASI 50, along with the number achieving PASI 50 on placebo out of the total number randomised to placebo. These were synthesised to estimate a baseline risk of achieving PASI 50 of 14.7% (95% credible interval: 12.4% to 17.1%). This translated to 1.0485 (95% CrI: 0.9486 to 1.153) on the probit scale.

Table 15. PASI 50 response rates associated with placebo used to estimate baseline risk

Study	No. achieving PASI 50	No. randomised	PASI 50
AMAGINE-1	17	220	7.7%
AMAGINE-2	47	309	15.2%
AMAGINE-3	57	315	18.1%
Papp 2012	6	38	15.8%
CHAMPION	16	53	30.2%
Asahina 2010	9	46	19.6%
PSOR-005	22	88	25.0%
ESTEEM 1	48	282	17.0%
ESTEEM 2	27	137	19.7%
Papp 2013	20	87	23.0%

Ohtsuki 2017	18	84	21.4%
LIBERATE	28	84	33.3%
Leonardi 2003	24	166	14.5%
Gottlieb 2003	6	55	10.9%
Papp 2005	18	193	9.3%
Van de Kerkhof 2008	4	46	8.7%
Bagel 2012	4	62	6.5%
Bachelez 2015	22	107	20.6%
Tyring 2006	43	306	14.1%
Yang 2012	6	45	13.3%
EXPRESS	6	77	7.8%
SPIRIT	11	51	21.6%
Torii 2010	2	19	10.5%
UNCOVER-1	50	431	11.6%
FEATURE	3	59	5.1%
ERASURE	22	246	8.9%
FIXTURE	49	324	15.1%
JUNCTURE	5	61	8.2%
PEARL	8	60	13.3%
PHOENIX 1	26	255	10.2%
PHEONIX 2	41	410	10.0%
LOTUS	32	162	19.8%
Igarashi 2012	4	31	12.9%
BRIDGE	38	131	29.0%

Section B: Clarification on cost-effectiveness data

Health-related quality of life

B1. Priority Question: Please provide justification for using a complete case analysis approach for EQ-5D data from the AMAGINE-1 trial.

a. Please tabulate the volume of missing EQ-5D data at each time point from baseline to week 12.

b. Please explain why imputation methods were not used for missing EQ-5D data.

Please find a summary of the missing EQ-5D values from baseline to week 12 in the AMAGINE-1 study in **Table *16*** below.

Table 16: Summary of missing EQ-5D values in AMAGINE-1 trial

Visit		Placebo	AMG827 140 mg Q2W	AMG827 210 mg Q2W	Total
BASELINE	N	220	219	222	661
	Number of missing values (%)	4 (0.6%)	3 (0.5%)	1 (0.2%)	8 (1.2%)
	Number of non-missing values (%)	216 (32.7%)	216 (32.7%)	221 (33.4%)	653 (98.8%)
WEEK 4	N	220	219	222	661
	Number of missing values (%)	11 (1.7%)	7 (1.1%)	10 (1.5%)	28 (4.2%)
	Number of non-missing values (%)	209 (31.6%)	212 (32.1%)	212 (32.1%)	633 (95.8%)
WEEK 8	N	220	219	222	661
	Number of missing values (%)	12 (1.8%)	16 (2.4%)	19 (2.9%)	47 (7.1%)
	Number of non-missing values (%)	208 (31.5%)	203 (30.7%)	203 (30.7%)	614 (92.9%)
WEEK 12	N	220	219	222	661
	Number of missing values (%)	15 (2.3%)	12 (1.8%)	13 (2.0%)	40 (6.1%)
	Number of non-missing values (%)	205 (31.0%)	207 (31.3%)	209 (31.6%)	621 (93.9%)

As can be seen in **Table *16***, at week 12 across treatment groups 6.1% of EQ-5D values (40/621) were missing. Moreover, descriptive analyses of EQ-5D based on both complete cases and using multiple imputation were presented as part of the clinical trial report and are summarised in **Table *17***. As the inferences from both analyses were very similar, the team opted for the simpler complete case analysis approach.

Table 17: Complete case vs multiple imputation analysis of EQ-5D values at week 12

	Placebo (N = 220)	Brodalumab	
		140 mg Q2W (N = 219)	210 mg Q2W (N = 222)
Complete case analysis			
Week 12			
Summary statistics			
N1	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

	Placebo (N = 220)	Brodalumab 140 mg Q2W (N = 219)	Brodalumab 210 mg Q2W (N = 222)
Q1, Q3	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Week 12 (Cont'd)			
Treatment difference			
LS mean		[redacted]	[redacted]
SE		[redacted]	[redacted]
(95% CI)		[redacted]	[redacted]
p-value		[redacted]	[redacted]
Multiple imputation			
Week 12			
Summary statistics			
N1	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]
(95% CI)	[redacted]	[redacted]	[redacted]
Week 12 (Cont'd)			
Treatment difference			
LS mean		[redacted]	[redacted]
SE		[redacted]	[redacted]
(95% CI)		[redacted]	[redacted]
p-value		[redacted]	[redacted]

Reference: Clinical Trial Report, Table 14-4.25.51.1

B2. Priority Question: Please provide details of the regression methods used on the individual patient data and the associated measures of goodness of fit in order to estimate change in EQ-5D from baseline to 12 weeks.

a. Please clarify whether correlation between utility values for one individual at different assessment points was taken into account, and whether a repeated measures model was used.

We can confirm that within-patient correlation between utility values at different visits was not taken into account and that a repeated measures model was not used for these analyses.

b. Please provide details on how the EQ-5D-5L was converted to the EQ-5D-3L.

We can clarify that version EQ-5D-3L of EQ-5D was used in the AMAGINE-1 trial and thus, no conversion was needed. The reference to EQ-5D-5L in Table 48 of the submission is a typo and should read "EQ-5D-3L."

c. Please provide justification for why the regression model adjusted for baseline DLQI and not baseline EQ-5D.

At the time of analysis, adjustment for baseline DLQI was proposed to align with similar, earlier submissions. We are grateful to have the opportunity to revisit and explore this aspect of the analysis in the next section.

B3. Priority Question: In order to assess alternative specifications of the EQ-5D regression model, please provide additional utility estimates (with uncertainty) and associated measures of goodness of fit for the following specifications:

a. EQ-5D regression model adjusted for baseline EQ-5D score.

b. EQ-5D regression model adjusted for baseline EQ-5D score and baseline PASI, with and without adjustment for baseline DLQI.

c. The above specifications (a. and b.) for the subgroup with a baseline DLQI > 10.

As requested, please find a summary of the additional utility estimates, with standard errors, and associated measures of goodness of fit for the alternative specifications of the EQ-5D regression model in Table 20 below. Please note that the models were estimated using the restricted maximum likelihood method. The parameter estimates for the intercept and PASI response categories are noticeably similar between the three models presented here. Of the three baseline covariates included in the model, only the parameter estimate associated with baseline EQ-5D is statistically significantly different from zero, based on a significance level of 5%, and so model B3a would be the most suitable for our analyses.

Table 18: Table 47a Parameter coefficients from ANOVA models, complete cases

	Model B3a		Model B3bi		Model B3bii	
ANOVA model	**Coefficient**	**Standard error**	**Coefficient**	**Standard error**	**Coefficient**	**Standard error**
All patients (scenario analysis, N=617)						
Intercept	0.3764	0.02151	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50–74	0.1611	0.03236	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75–89	0.2668	0.02834	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90–99	0.2932	0.02467	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	0.3023	0.02208	[redacted]	[redacted]	[redacted]	[redacted]
Baseline EQ-5D	-0.6226	0.02784	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI			[redacted]	[redacted]	[redacted]	[redacted]
Baseline DLQI					[redacted]	[redacted]
-2 Res Log Likelihood	-143.1		[redacted]		[redacted]	
AIC (Smaller is Better)	-141.1		[redacted]		[redacted]	
AICC (Smaller is Better)	-141.1		[redacted]		[redacted]	
BIC (Smaller is Better)	-136.7		[redacted]		[redacted]	
DLQI>10 (base case analysis, N=401)						
Intercept	0.3408	0.02560	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50–74	0.2302	0.04226	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75–89	0.3376	0.03805	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90–99	0.3573	0.03245	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	0.3739	0.03105	[redacted]	[redacted]	[redacted]	[redacted]
Baseline EQ-5D	-0.6480	0.03531	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PASI			[redacted]	[redacted]	[redacted]	[redacted]
Baseline DLQI					[redacted]	[redacted]
-2 Res Log Likelihood	-16.7		[redacted]		[redacted]	
AIC (Smaller is Better)	-14.7		[redacted]		[redacted]	
AICC (Smaller is Better)	-14.7		[redacted]		[redacted]	
BIC (Smaller is Better)	-10.7		[redacted]		[redacted]	

ANOVA, analysis of variance; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index.

Using the coefficients from model B3a described in **Table *18***, new utilities have been estimated (**Table *19***). The ICERs for the comparison of brodalumab (sequence 1) versus DMF (sequence 9) using these alternative utility values are also presented for each patient group. Both ICERs are slightly lower than the ICERs in the equivalent scenarios presented in the submission.

Covariance matrices, for use in the probabilistic sensitivity analysis of the economic model, have been provided for the all patient and DLQI>10 at baseline patient groups in **Table *20*** and **Table *21***, respectively.

Table 19. Health state utility values estimated from model B3a, adjusting for baseline EQ-5D

Utility by PASI response category		Patients with DLQI>10 at baseline	All patients
Baseline		0.5206	0.6105
Mean change	PASI<50	0.0035	-0.0037
	PASI 50–74	0.2337	0.1574
	PASI 75–89	0.3411	0.2631
	PASI 90–99	0.3608	0.2895
	PASI 100	0.3774	0.2986
ICER: BRO vs DMF		£12,850	£15,647

Table 20. Covariance matrix for model B3a (all patients)

Variable	Intercept	PASI 100	PASI 50-74	PASI 75-89	PASI 90-99	PASI 0-49	EQ5D BL
Intercept	0.000463						
PASI 100	-0.00016	0.000487					
PASI 50-74	-0.00017	0.000179	0.001047				
PASI 75-89	-0.00016	0.000180	0.000179	0.000803			
PASI 90-99	-0.00018	0.000179	0.000179	0.000179	0.000609		
PASI 0-49*							
EQ5D BL	-0.00047	-0.00003	-7.05E-6	-0.00003	-4.46E-6		0.000775

Table 21. Covariance matrix for model B3a (DLQI>10 at baseline)

Variable	Intercept	PASI 100	PASI 50-74	PASI 75-89	PASI 90-99	PASI 0-49	EQ5D BL
Intercept	0.000656						
PASI 100	-0.00031	0.000964					
PASI 50-74	-0.00030	0.000322	0.001786				
PASI 75-89	-0.00028	0.000323	0.000324	0.001448			
PASI 90-99	-0.00032	0.000321	0.000321	0.000321	0.001053		
PASI 0-49*							
EQ5D BL	-0.00065	-0.00002	-0.00004	-0.00008	1.748E-6		0.001247

B4. Priority Question: To assess the generalisability of the EQ-5D data reported in the AMAGINE-1 trial to the AMAGINE-2 and AMAGINE-3 trials, please provide

additional comparisons across these trials for mapping between DLQI and EQ-5D. Please present EQ-5D estimates for each PASI outcome separately for each trial (AMAGINE-1, 2 and 3) using a published and validated mapping function.

Table 22 presents DLQI scores at baseline and mean change in DLQI scores from baseline to week 12 for patients achieving different levels of PASI response as observed in AMAGINE-1, AMAGINE-2 and AMAGINE-3. Results are presented for the subgroup of patients with a DLQI score of greater than 10 at baseline as well as for all patients, regardless of baseline DLQI. EQ-5D utility values were generated for each patient group achieving each PASI outcome from each AMAGINE trial using 3 published mapping functions.

- A study by Knight et al. (2012)[5] was identified in the systematic review of HRQoL studies. The authors used data from a scatter plot published by Woolacott et al. (2006)[6] to quantify the relationship between EQ-5D scores and DLQI. The result was EQ-5D = 0.956-0.0248*DLQI.

- The manufacturer submission to NICE for TA180 (ustekinumab) reported the results of two regressions to inform the relationship between EQ-5D and DLQI.

    1. The authors used data from the scatter plot published by Woolacott et al. (2006). The results of their ordinary least squares (OLS) regression was quantified as EQ-5D = 0.8554 – 0.0162*DLQI.

    2. The authors validated the above results against the results of an independently conducted linear regression analysis relating EQ-5D to DLQI observed in 3,500 psoriasis patients in Germany, which was quantified as EQ-5D = 0.908-0.016*DLQI.

Although there are differences between utility values generated by the different published mapping algorithms, there is broad agreement between the results estimated from the different AMAGINE trials. This reflects the broad agreement between changes in DLQI by PASI response category in the three AMAGINE RCTs.

Table 22 also presents the ICERs for the comparison of brodalumab (sequence 1) vs DMF (sequence 9), the sequence with the lowest total costs and QALYs, using each possible regression equation, AMAGINE trial and patient group. Across all tested values, the ICER never goes over £30,000 per QALY gained. The brodalumab sequence also consistently dominates the sequences starting with adalimumab, infliximab, ustekinumab and secukinumab and extendedly dominates the sequences starting with apremilast and etanercept.

AR049_01: Extra analyses prepared for mapping of DLQI to EQ-5D
EXTENDED! Population with B/L DLQI > 10: FAS, DLQI baseline and DLQI week 12 available

Table 22. EQ-5D utility values generated for each PASI outcome from each AMAGINE trial using published mapping functions

PASI response category		Mean DLQI Scores			Mean EQ-5D Scores									
					Submitted model	Knight 2012			TA180 (Ustekinumab) Manufacturer Submission			TA180 (Ustekinumab) Manufacturer Submission		
						EQ-5D=0.956-0.0248*DLQI			EQ-5D=0.8554-0.0162*DLQI			EQ-5D=0.908-0.016*DLQI		
		AMAGINE-1	AMAGINE-2	AMAGINE-3		AMAGINE -1	AMAGINE-2	AMAGINE-3	AMAGINE -1	AMAGINE-2	AMAGINE-3	AMAGINE -1	AMAGINE-2	AMAGINE-3
Patients with DLQI>10 at baseline														
Baseline		[redacted]	[redacted]	[redacted]	0.5206	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change	PASI<50	[redacted]	[redacted]	[redacted]	0.0158	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PASI 50-74	[redacted]	[redacted]	[redacted]	0.1898	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PASI 75-89	[redacted]	[redacted]	[redacted]	0.2946	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PASI 90-99	[redacted]	[redacted]	[redacted]	0.3552	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PASI 100	[redacted]	[redacted]	[redacted]	0.368	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER: BRO vs DMF					£13,353	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All patients														
Baseline		[redacted]	[redacted]	[redacted]	0.6105	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change	PASI<50	[redacted]	[redacted]	[redacted]	0.0044	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PASI 50-74	[redacted]	[redacted]	[redacted]	0.1349	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PASI 75-89	[redacted]	[redacted]	[redacted]	0.2441	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PASI 90-99	[redacted]	[redacted]	[redacted]	0.2798	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PASI 100	[redacted]	[redacted]	[redacted]	0.2897	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER: BRO vs DMF					£16,444	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Best Supportive Care (BSC)

B5. Priority Question: Please provide a break-down of the resource use and unit cost values used to estimate annual costs of (i) medication and (ii) inpatient admissions and outpatient care associated with BSC.

a. Please tabulate each element of resource use derived from Fonia et al., (2010) separately and include:

i. The unit cost applied to these elements.

ii. Before and after inflation indexing and provide details of index used.

iii. Pre- and post-biologics.

Table *23* presents inpatient and outpatient elements of healthcare resource use and 2008-09 unit costs as reported in Fonia *et al.* 2010[7,8]. The table also presents the reported total costs in the 12 months preceding and 12 months following biologic therapy initiation, using 2008-09 values. **Table *24*** presents the biologic, systemic and supportive drug utilisation, unit costs and total costs (at 2008-09 values) among patients in the year prior to and year following biologic therapy initiation.

Total costs of inpatient and outpatient care and drug utilisation accrued in the 12 months prior to biologic therapy initiation were inflated to 2016-17 values using the Special Aggregate: 06 Health component of the Consumer Price Index from the Office of National Statistics.[9] These values were then used as inputs for the cost of best supportive care in the economic model.

Table 23 Cost of inpatient and outpatient admissions & hospital resource use 12 months before and 12 months after biologic therapy initiation

Resource	Unit cost (£)	12 months before biologics initiation			12 months after biologics initiation	
		Mean resource units [days] (± SE) per patient	Mean cost £ (± SE) per patient	Mean cost £ per patient (inflated CPIH INDEX [3])	Mean resource units [N] (± SE) per patient	Mean cost £ (± SE) per patient
Inpatient admissions	291 per day	6.49 (1.99)	1887.7 (578.4)	2370.44	1.55 (0.71)	451.8 (206.3)
ICU admissions	1072 per day	-	-	-	-	-
HDU admissions	676 per day	-	-	-	-	-
A&E visits	86 per visit	0.03 (0.03)	2.26 (2.26)	2.84	0.04 (0.03)	3.39 (2.52)
Outpatient visits	72 per visit	3.22 (0.11)	232.1 (8.0)	291.45	3.25 (0.09)	234.0 (6.8)
Day ward admissions	441 per admission	0.14 (0.05)	63.8 (22.9)	80.12	1.16 (0.22)	510.6 (98.1)
Phototherapy	283 per session	2.76 (1.20)	770.8 (336.0)	966.91	0.26 (0.26)	74.5 (74.5)

Total			**2956.7 (758.8)**	**3711.76**		**1274.3 (240.2)**

Source: Fonia *et al.* 2010 and Fonia *et al*. 2014. A&E, Accident & Emergency visits; HDU, High Dependency Unit Admissions ICU, Intensive Care Unit; N, Number of patients; SE, Standard Error

Table 24. Cost of drugs 12 months before and 12 months after biologic therapy initiation

Resource	Daily cost of treatment (£)	Unit cost per mg (£)	12 months before biologics initiation		12 months after biologics initiation	P-value
			Mean cost £ (± SE) per patient	Mean cost £ (± SE) per patient (inflated CPIH INDEX [3])	Mean cost £ (± SE) per patient	
Biologic drugs						
Adalimumab	26.52	0.94	-		405.3 (190.6)	
Efalizumab	24.17	1.35	-		464.8 (209.5)	
Etanercept	25.54	3.58	-		6920.1 (619.9)	
Infliximab	32.28	420	-		2633.0 (535.4)	
Total biologics					10423.3 (37.4)	
Systemic drugs						
Acitretin	1.9	0.04	81.0 (20.3)	101.71	10.1 (7.7)	<0.001
Ciclosporin	5.25	0.02	628.9 (97.5)	789.73	212.5 (67.7)	<0.001
Fumaric acid esters	14.82	0.021	509.5 (150.6)	639.79	43.8 (25.7)	<0.001
Hydroxycarbamide	0.08	0.0002	3.6 (1.8)	4.52	-	
Methotrexate	0.07	0.05	15.5 (3.4)	19.46	11.9 (6.2)	0.144
Mycophenolate mofetil	10.07	0.003	10.8 (7.2)	13.56	-	
Total systemic drugs			1249.4 (179.5)	1568.78	278.2 (70.9)	<0.001
Supportive drugs						
Aciclovir	-	0.0003	-		-	
Amoxicillin	-	0.0002	0.05 (0.05)	0.06	-	
Augmentin	-	0.0006	-		0.10 (0.10)	
Ciprofloxacin	-	0.0002	-		0.03 (0.03)	
Erythromycin	-	0.0007	0.20 (0.20)	0.25	-	
Flucloxacillin	-	0.004	0.74 (0.74)	0.93	4.63 (2.96)	0.314
Hydrocortisone	-	0.0009	-		0.28 (0.28)	
Metronidazole	-	0.0001	-		-	
Prednisolone	-	0.01	0.15 (0.12)	0.19	0.18 (0.17)	1
Rifinah 300	-	0.0009	-		0.28 (0.28)	

Total supportive drugs			1.14 (0.77)	1.43	5.50 (3.29)	0.744
Total			**1250.5 (179.5)**	**1570.21**	**10707.0 (396.2)**	**<0.001**

Source: Fonia *et al.* 2010 SE, Standard Error; mg, milligram

b. Please state all assumptions that were used to estimate the costs of BSC.

- The annual cost of BSC was based on the sum of the drug costs and the costs of inpatient admissions and outpatient care over the 12 months prior to biologic therapy initiation to reflect costs for how moderate to severe patients are managed in the absence of biologic treatment.
- The mean drug cost captures the total costs of systemic and supportive drugs.
- The mean cost of inpatient admissions and outpatient care captures inpatient, intensive care unit and high dependency unit admissions; accident and emergency visits; outpatient visits; day ward admissions; and phototherapy.
- Prices were inflated based on the CPIH INDEX 06 from 2008 to 2017.
- Inflation index was 82.9 for 2008 and the average (=104.1) of 103.4 for Q1 2017 and 104.8 for Q2 2017.
- Inflation index was calculated as follows :104.1/82.9=1.25573
- All 2008 values were multiplied by the inflation index to reflect current values.

Effect modification

B6. Please provide details on how scenario 4A (page 146) was implemented in the model.

a. Please clarify whether the adjustment was applied to all lines of therapy or only second and third lines

The adjustment was applied to second and third lines only.

b. Please clarify whether the adjustment was applied to all treatments or only biological therapy.

The adjustment was applied to any treatment used second or third in the sequence, but not to best supportive care.

Section C: Textual clarifications and additional points

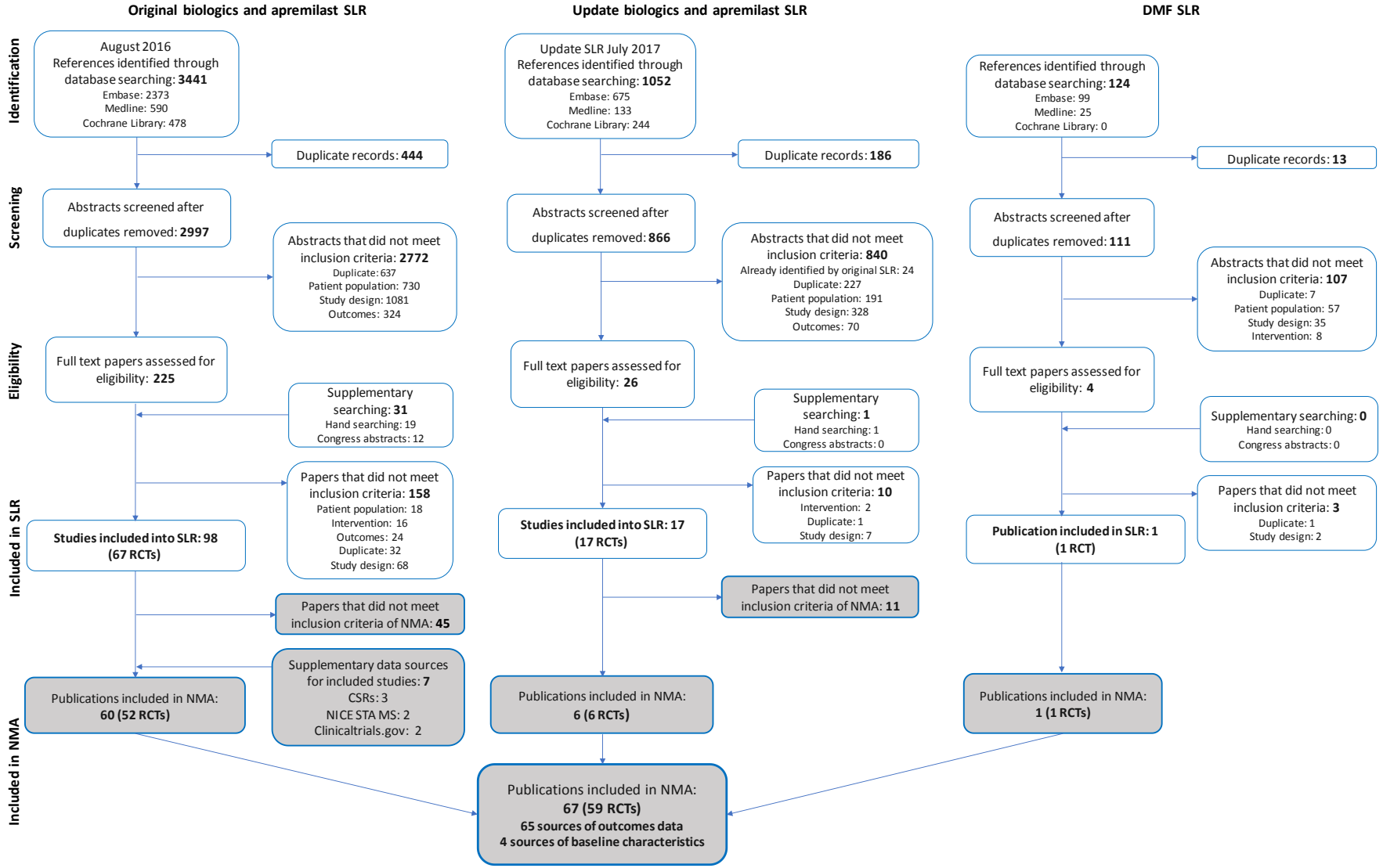
C1. Please clarify whether the pack cost for Apremilast reported in Table 50 should read £265.18 rather than £256.18.

Yes, this is an error. It should read £265.18.

C2. The numbers in n Figure 33 (PRISMA diagram) do not appear to add up. In the 'original biologics and apremilast SLR' flow diagram, 225 full text papers were assessed for eligibility with an additional 31 records identified by supplementary searching; 150 records did not meet inclusion criteria, therefore, 106 records should have been included in the SLR, rather than 98. Please explain the discrepancy. In the 'update biologics and apremilast SLR', 17 RCTs were included in the SLR. Twelve did not meet inclusion criteria of NMA, which should have left 5 RCTs included in the NMA, rather than 6, as reported in the flow chart. Again, please explain the discrepancy.

Both discrepancies were errors. Eight records in the original review were excluded at a late stage and the PRISMA diagram had not been updated to reflect this. In the SLR update, we erroneously counted the study by Reich et al. (2017)[10] twice as it reports on 2 RCTs (reSURFACE 1 and reSURFACE 2), only one of which was included in the NMA. **Figure *1*** presents a corrected PRISMA diagram.

Figure 1. CORRECTED PRISMA flow diagram for clinical evidence SLR



C3. Please explain why figures in Section D.1.2 (Figure 34 to Figure 36) do not always add up (e.g. received IP n=297, completed phase n=274, entered rescue n=0, discontinued phase n=22) and send corrected figures, if appropriate.

The numbers do not add up because the underlying definitions are not made to provide a full breakdown. This is described in the notes to the relevant tables in the clinical study reports, here showing AMAGINE-2, table 14-1.1.2:

- Completing the maintenance phase is defined as having a study assessment on or after study day 351 without entering rescue phase
- Discontinuation during current phase is defined as entering the phase and termination from study during that phase

This means that a patient could be defined as neither completing nor discontinuing the trial.

Figure 36 was copied from the Papp *et al.* 2016 publication of AMAGINE-1. By mistake, the legend to the figure was not copied over, but is included in Fig S2 in appendix S2 of the publication (available at https://doi.org/10.1111/bjd.14493). The legend addresses two apparent inconsistencies indicated by "*" in the figure:

- *One patient from the placebo/brodalumab 210 mg group and one patient from the brodalumab 140 mg/210 mg (non-rerandomized) group are missing because they did not have a week 52 assessment; these patients were not considered as having completed the study, nor were they considered as having discontinued.

Similarly, in Figure 34, one patient from the placebo/brodalumab 210 mg group is missing because they met neither the definition or completion nor the definition of discontinuation.

In Figure 35, one patient from the placebo/brodalumab 210 mg group is missing as are two patients from the ustekinumab/ustekinumab group because they failed to meet the definition of completion or discontinuation.

The source for the numbers is provided below as reference to table number in the corresponding clinical study report.

Re Figure 34, Patient disposition in AMAGINE-2

Table	Title
14-1.1.1.	"Subject disposition During the Induction Phase Brodalumab Study 20120103 Full Analysis Set", p. 252 + p. 256
14-1.1.2.	"Subject Disposition During Maintenance Phase Brodalumab Study 20120103 Efficacy Analysis Set – Maintenance Phase", p. 258 + p. 263

Re Figure 35, Patient disposition in AMAGINE-3

Table	Title

14-1.1.1.	”Subject disposition During the Induction Phase Brodalumab Study 20120104 Full Analysis Set”, p. 240 + p. 244
14-1.1.2.	“Subject Disposition During Maintenance Phase Brodalumab Study 20120104 Efficacy Analysis Set – Maintenance Phase”, p. 246 + p. 251

Re Figure 36, Patient disposition in AMAGINE-1

Table	Title
14-1.1.1	Subject Disposition During the Induction Phase. Full Analysis Set, p. 220 + p. 223
14-1.1.2.1	Subject Disposition for Non-rerandomized Subjects During the Withdrawal Phase. Efficacy Evaluable Subset for the Withdrawal Phase (Non-rerandomized Subjects), p. 225 + p. 228
14-1.1.2.2	Subject Disposition for Rerandomized Subjects During the Withdrawal Phase. Efficacy Evaluable Subset for the Withdrawal Phase (Rerandomized Subjects), p. 230 + p. 233

[1] Papp et al. Brodalumab, an anti-interleukin-17-receptor for psoriasis.(2012) New England Journal of Medicine 366;13;1181:1189
[2] Nakagawa et al. 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 (2016) Journal of Dermatological Science 81: 44-52.
[3] Krueger et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. (2007) New England Journal of Medicine 356; 6: 580-92.
[4] Dias et al. Evidence Synthesis for Decision Making 5 (2013). Medical Decision Making 33;5: 657-670.
[5] Knight et al. Cost-effectiveness of treatment with etanercept for psoriasis in Sweden (2012). European Journal of Health Economics. 13:145-56.
[6] Woolacott et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review (2006). Health Technology Assessment 10;46: 1-233.
[7] Fonia et al. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis (2010). British Journal of Dermatology 163;4: 807-816.
[8] *Erratum* (2014). British Journal of Dermatology 170;1: 226.
[9] Office of National Statistics, *Time series: CPIH INDEX 06 : HEALTH 2015=100.* 2017. Available at https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/l528/mm23.
[10] Reich et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials (2017). Lancet 390 (10091): 276-288.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Brodalumab for treating moderate to severe plaque psoriasis [ID878]

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.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- 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 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis Association
3. Job title or position	[redacted]
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 (6,000 registered users), and Social Media (12,000 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 (550,000 visitors in 2016) telephone helpline (1,000 enquiries in 2016) online forums (6,000 registered users in 2016) social media channels (including Facebook Group, Twitter and Instagram, 12,000 people in 2016)
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. Being a once a fortnight injection it does not impact too greatly on a patient's 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.

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?	
Topic-specific questions	
14. Topic-specific questions to be added here if required.	

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.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Brodalumab for treating moderate to severe plaque psoriasis [ID878]

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.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- 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 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
3. Job title or position	[redacted]
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 brodalumab.

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?	Psoriasis for many people can be a mild condition, which often follows a pattern of flare and remission. For most, at this mild level, topical therapies tend to work, although they can be very messy and often people find it difficult to use the products as prescribed on a regular basis, at this primary level. Therapies such as UV light can also be effective, but availability and the need to attend regular sessions at a centre can be problematic for those who work, are in education or have mobility issues. As psoriasis is a chronic condition, this mild level of psoriasis, if untreated, can start to progress and then be a more widespread moderate to severe form of psoriasis. For some who are dedicated, moderate psoriasis can still be managed, but often it is too widespread to consistently self-treat topically, and people feel that it is getting worse or the therapies are not working and it starts to become more severe. This situation often leads people to become anxious and frustrated, 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. Another problem that is often highlighted is the cracking and bleeding of the skin when scratched, which again can soil sheets and clothes and make people feel very low and depressed. A neglected aspect is the associated pain that people endure, tight inflamed skin can be very painful and people often describe it as similar to being sunburnt, with contact to heat or the cold making the pain very severe. At this stage, referral to secondary care and escalation of therapy is often needed. Most commonly a DMARD such as methotrexate will be offered. This is particularly feared by patients, for a number of reasons. Many people are frightened of its use, as they see it as a cancer therapy, the side effects are

	worrying and particularly the chance of hair loss, increased risk of infection and a common concern is the restriction of alcohol. The latter may appear to be of little significance in the face of getting better, but our experience is that this restriction to peoples' lifestyle has a profound effect, and they feel more isolated and feel that their life is being blighted, and will for this reason, often not take the therapy regularly. This highlights the complex relationship many people express to us about living with psoriasis. The desire to be (what they perceive is) normal, but struggling to cope with the therapies offered, due to their inconvenience or adverse event profiles. Psoriasis is a lonely disease in a world where people are judged by appearance. For some this can have profound psychological impact and lead to withdrawal of activities where skin is exposed, such as swimming or close contact with others due to potential rejection as often people are revolted by the appearance of psoriasis.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	For most the treatments do work and provide relief, but for some the therapies either don't work, cause adverse events or are too inconvenient to even contemplate.
8. Is there an unmet need for patients with this condition?	Although over recent years the psoriasis population has seen a wealth of new therapies becoming available, there is often a point where these stop being effective and an individual has exhausted the range of therapies, therefore there is still a need to find some form of alternate treatment.

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 biologic agents (every two-weeks) with a different target IL-17 receptor, so could be an advantage in those who have had no response to other biologic agents against other targets.
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. There is a prescribing warning about patients with a history of depression and suicide ideation, so potentially that could be a disadvantage for this group, given the often reported increased association of depression amongst people with psoriasis.
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.	None as far as we can see.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Not that we are aware.
Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Topic-specific questions	
14.Topic-specific questions to be added here if required.	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. • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Brodalumab for treating moderate to severe plaque psoriasis [ID878]

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

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- 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 (BAD)**

3. Job title or position	**Consultant Dermatologists**
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' Physician's Global Assessment rating • Reducing the impact of the disease on quality of life • Control of psoriatic arthritis, where relevant

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 2017 BAD guidelines on biologic therapies for psoriasis (*in press*), 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 (Iskandar IYK, Ashcroft DM, Warren RB, Evans I, McElhone K, Owen CM, Burden AD, Smith CH, Reynolds NJ, Griffiths CEM. 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; Warren RB, Smith CH, Yiu ZZN, Ashcroft DM, Barker JNWN, Burden AD, Lunt M, McElhone K, Ormerod AD, Owen CM, Reynolds NJ, Griffiths CEM. 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. 2. In moderate psoriasis, i.e. those who would fulfil the licensed indications for biologic therapy (including brodalumab) but not necessarily NICE criteria, there are very few options and yet the disease can still have a very major impact on quality of life 3. People with severe psoriasis at localised sites, i.e. high-need areas such as face, hands, feet, flexural/genital sites, will not have a PASI 10 but nevertheless will have disease with very major impact.
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; apremilast; fumaric acid esters; standard systemic therapies (see NICE CG153).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BAD guideline for biologic therapy for psoriasis (***in press***) http://onlinelibrary.wiley.com/doi/10.1111/bjd.15665/full NICE CG153 www.nice.org.uk/guidance/cg153 ➔ In the final scope, please refer to NICE CG153 accurately (i.e. corticosteroids/vitamin d as first line), also updated in 2016/7 ➔ Phototherapy/systemic therapy for disease that is extensive (10% or more) – i.e. this group cannot usually be managed adequately with topical therapy alone (again please refer to CG153 accurately) ➔ There should also 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.

	Additionally, the final scope mentions that “most treatments reduce severity 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 severity….”) as many of the new biologic treatments do clear or nearly clear the disease and maintain it in this state. Finally, please add “people with and without psoriatic arthritis”, and “people who are and not obese” to the “Other considerations” section for consideration of population subgroups.
• 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 Iskandar IY, Ashcroft DM, Warren RB, Yiu ZZ, McElhone K, Lunt M, Barker JN, Burden AD, Ormerod AD, Reynolds NJ, Smith CH, Griffiths CE. 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.
• 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. IL17 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	Yes – biologic therapy is a well-established intervention in psoriasis.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	There would not be any expected differences in health resource use compared to existing NICE-approved agents.
• 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	N/A

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Potentially yes, by providing an additional treatment option for this major, chronic debilitating disease.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As per label, caution should be exercised in people with inflammatory bowel disease (may potentially worsen disease).
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	Biologic therapy has been available on the NHS for people with moderate-to-severe psoriasis who meet the eligibility criteria.

treatments needed, additional clinical requirements, factors affecting patient acceptability 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 2017 BAD guidelines (*in press*) 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
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?	The calculation of the QALY does not encompass time off work or other limitations that psoriasis imposes (e.g. social isolation, avoidance of relationships, stigma, depression, anxiety). Furthermore, the DLQI is often mapped to EQ5D but whilst important, the DLQI doesn't capture anxiety and depression (which are common in psoriasis); we also know that the mapping algorithms are not necessarily accurate (*paper submitted for publication using EQ5D and DLQI data from pharmacovigilance registry BADBIR*)
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	This is the first IL17 receptor antagonist, although two anti-IL-17A monoclonal antibodies have been NICE-approved (secukinumab and ixekizumab).

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Antagonism of the IL17 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?	Mild candida infection has been reported with IL17 inhibition; infections and rare adverse effects are comparable to those seen with other biologic therapies generally. Brodalumab seems to have a comparable safety profile with other IL17 inhibitors and biologic therapies in general.
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?	• **Psoriasis symptoms 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:** specifically, also candida 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	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

but have come to light subsequently?	ensure we can capture high quality pharmacovigilance data and make relevant comparisons with other biologic agents (N.B. > 12,000 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]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No; however, ciclosporin cannot be used for > 1 year and is therefore not a relevant comparator for this STA.
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.
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in	

opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Important new technology
- High efficacy rates
- 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.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Brodalumab for treating moderate to severe plaque psoriasis [ID878]

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

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- 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 Dermatological Nursing Group**

3. Job title or position	**Dermatology Clinical Nurse Specialist**
4. Are you (please tick all that apply):	**x**☐ 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).	I work for the NHS and I am a member of the British Dermatological Nursing Association which is a charitable organisation.
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,	The main aim of the treatment is to significantly improve the signs, symptoms and psychological impact that psoriasis has on the patient, improving 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.)	For the skin to be more than 90% clear of psoriasis.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Patients with pustular psoriasis, palmoplantar psoriasis and scalp psoriasis do not have as many licenced treatment options for their specific conditions. Some patients have also got so used to their skin disease and when completing the Dermatology Life Quality Index give a low score which results in the medication being declined.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Currently patients are offered topical treatments, phototherapy, methotrexate, ciclosporin, acitretin, apremilast and other biologics.
• Are any clinical guidelines used in the treatment of the	NICE Guidelines, Methotrexate Guidelines by the BAD, Biologic Guidelines by the BAD.

condition, and if so, which?	
• 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.)	There is a well-defined pathway for treatment for psoriasis on NICE Clinical Guidelines 153 (2012).
• What impact would the technology have on the current pathway of care?	It would give another option for patients whose disease is not controlled or who have adverse reactions on current options.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, it will be used in the same way as current care following NICE CG.
• How does healthcare resource use differ between the technology and current care?	There should be no difference apart from efficacy for some patients.
• In what clinical setting should the technology be	Secondary Care, to enable close monitoring by those with specialist training and experience with this group of drugs.

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training for staff in secondary care in understanding the products and how it works and its associated risks. Training for healthcare providers who arrange delivery of the medication and nursing support for the patients, in their own home.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, not all patients have an effective response to current treatments available.
• Do you expect the technology to increase length of life more than current care?	Not necessarily.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes for some patients who have not had a good response to current approved treatment options.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It may be more effective for some groups who are not controlled well on current treatments. There may be some patients who will not respond to the treatment, everybody responds differently to each medication. There will be some that it will not be as effective for, but this will not be known until the patient has commenced the medication.
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 or ease of use or additional tests or monitoring needed.)	The technology should not be any more difficult to use than current treatments. Some patients are needle phobic and require nursing support or for a family member or friend to be trained in the administration of the medication. Some patients may require additional concomitant treatment if the treatment isn't effective or if they have unstable psoriasis they may need to continue on their current systemic medication for a few weeks as long as there are interactions with concurrent medication and no adverse reactions.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, as per NICE CG and Specific Product Characteristics (SPC) and BAD Guidelines.
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?	Not known, and will only be discovered by monitoring patients.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Potentially, yes. It will be another option for patients, each patient with psoriasis responds differently to medication.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	It will give an additional option for patients that react or do not respond to current treatment options available.
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?	It depends on the side effects and adverse effects.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	

• 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?	Not known as I have no current experience with this drug.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator	

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- To have a technology that significanly improves psorasis
- To have an out come of 90% plus improvement
- To have another treatment option for patients with moderate to severe psoriasis
- For patients to have a choice of who administers the treatment.
- Consider revising the PASI score to ensure easier access for patients with severe disease.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Brodalumab for treating moderate to severe plaque psoriasis [ID878]

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

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- 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	[redacted]

3. Job title or position	[redacted]
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).	**British Society of Rheumatology**
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,	The aim of treatment in psoriasis is to control skin inflammation to improve symptoms such as pain and itch as well as improving quality of life for patients. Around 20% of patients with psoriasis also have psoriatic arthritis, an inflammatory arthritis so many patients are co-managed by dermatology and rheumatology.

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.)	The British Association of Dermatologists and most published studies advise that a clinically significant response is a PASI75 which is a 75% decrease in the psoriasis area and severity index (PASI). This represents a significant decrease in the area, erythema, induration and scaling of psoriasis all over the body.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – although many more therapies have become available over the last decade, a significant proportion of patients do not respond to the therapies available at present and newer therapies are required. Brodalumab reduces IL-17 (similar to secukinumab and ixekizumab) but does this using a different mode of action (as a receptor antagonist rather than a monoclonal binding antibody) so it may be effective even when existing IL-17 therapies do not work.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Psoriasis is currently treated using topical therapies (for very mild disease only), light therapy, standard oral therapies (such as methotrexate or cyclosporin) and biological therapies (TNF inhibitors, IL12/23 inhibitor and IL17A inhibitors).
• Are any clinical guidelines used in the treatment of the	Dermatologists predominantly follow the British Association of Dermatology guidelines. This supports the use of either ustekinumab, adalimumab or secukinumab as first line biologics once standard therapies have been failed. Physician obviously have to abide by the NICE TAs for the use of biologics in England. NICE

condition, and if so, which?	and the BAD guidelines recommend switching to alternative biologics if these are not effective and brodalumab could be used.
• 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.)	The pathway is quite well defined. Those with moderate to severe psoriasis would be required to fail two standard therapies (either phototherapy or oral disease modifying agents such as methotrexate/cyclosporin) prior to access to biologics. They are also required to have certain severity markers such as PASI score and DLQI scores.
• What impact would the technology have on the current pathway of care?	This technology would offer a different mode of action in psoriasis targeting the important IL17 pathway. The access to biologics would likely remain the same but this would be another option for therapy alongside previously approved biologics
10. 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?	Resource use would be similar. Brodalumab is given as a subcutaneous injection as are most of the approved biologic therapies so patients usually have one training session on how to give the injection and then self-administer at home. Pre-therapy infection screening and ongoing safety monitoring with blood tests is the same as existing biologic therapies for psoriasis.
• In what clinical setting should the technology be	Secondary care dermatology

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nothing. This would fit into existing clinical care models.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – this drug provides a new option for patients that may not have responded to existing therapy.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	No, the improvement in QoL is generally significant across all of the biologic therapies at a group or population level. However some individuals respond to one biologic when they do not respond to another. Brodalumab offers a unique mode of action and may therefore allow an increase in HR-QoL for individuals who would not have responded to some other therapies.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
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 or ease of use or additional tests or monitoring needed.)	Same as existing biologics. Similar pre-treatment screening (for TB and hepatitis) and similar ongoing safety monitoring (regular routine blood tests and annual skin checks)

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I presume that access to brodalumab would be similar to other biologics requiring moderate to severe psoriasis to be eligible for treatment (based on PASI and DLQI, failed standard therapy) and then treatment would only be continued if a PASI response is achieved.
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?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	No

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?	Yes – it has a unique mode of action so could provide efficacy where other therapies have failed.
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?	Generally speaking brodalumab and the biologic therapies are well tolerated by patients. Risks and side effects are similar to existing therapies such as secukinumab. The most commonly seen side effects are infections which are a known risk and usually treated easily with antibiotics. IL17 inhibitors have a particular issue with causing candida infection but in the studies, these usually resolve with anti-fungal therapy.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – similar entry criteria to those stipulated by NICE for similar biologic therapy TAs

• 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?	Quality of life and proportions of patients achieving clearance or high response to therapy.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
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]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient expert statement

Brodalumab for treating moderate to severe plaque psoriasis in adults [ID878]

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 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.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- 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 10 pages.

About you	
1.Your name	**David Chandler**
2. Are you (please tick all that apply):	✓☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	The Psoriasis and Psoriatic Arthritis Alliance
4. Did your nominating organisation submit a submission?	✓☐ yes, they did ☐ no, they didn't ☐ I don't know
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)	✓☐ 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
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and	

care available on the NHS?	
10. Is there an unmet need for patients with this condition?	
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	
Patient population	
13. 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.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • • • • •	

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.

NICE National Institute for Health and Care Excellence

Patient expert statement

Brodalumab for treating moderate to severe plaque psoriasis in adults [ID878]

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 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.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- 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 10 pages.

About you	
1.Your name	**Helen McAteer**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Psoriasis Association
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
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)	☒ 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
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	
10. Is there an unmet need for patients with this condition?	
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	
Patient population	
13. 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.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • •	

-
-
-

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.

CONFIDENTIAL UNTIL PUBLISHED

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

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

Authors
Emily South, Research Fellow, CRD
Ros Wade, Research Fellow, CRD
Alessandro Grosso, NIHR Research Methods Fellow, CHE
Pedro Saramago Goncalves, Research Fellow, CHE
Laetitia Schmitt, Research Fellow, CHE
Claire Rothery, Senior Research Fellow, CHE
Kath Wright, Information Service Manager, CRD
Stephen Palmer, Professor of Health Economics, CHE

Correspondence to Ros Wade, Research Fellow, CRD, University of York, York YO10 5DD

Date completed 23/11/2017

Source of funding
This report was commissioned by the NIHR HTA Programme as project number 16/168/10.

Declared competing interests of the authors
None.

Acknowledgements
We would like to thank Dr Ruth Murphy, Consultant Dermatologist at Sheffield Teaching Hospitals NHS Foundation Trust for clinical advice.

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:

South E, Wade R, Grosso A, Saramago Goncalves P, Schmitt L, Rothery C, Wright K, Palmer S. Brodalumab for treating moderate to severe plaque psoriasis: A Single Technology Appraisal. CRD and CHE Technology Assessment Group, 2017.

Contributions of authors

Emily South and Ros Wade wrote the clinical effectiveness sections of the report and Ros Wade took overall responsibility for the clinical effectiveness sections. Alessandro Grosso, Stephen Palmer and Claire Rothery undertook the critique of the cost-effectiveness submission and contributed to the additional economic analyses. Laetitia Schmitt validated the company model and conducted the additional ERG analyses. Pedro Saramago Goncalves undertook the critique of the company network meta-analysis and conducted the additional ERG syntheses. Stephen Palmer 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.

Table of Contents

Table of Tables

Table of Figures

List of abbreviations

BAD	British Association of Dermatologists
BID	Twice daily
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CG	Clinical Guideline
CI	Confidence interval
CS	Company's submission
CSR	Clinical study report
DIC	Deviance Information Criterion
DLQI	Dermatology Life Quality Index
DMARDs	Disease-modifying anti-rheumatic drugs
DMF	Dimethyl fumarate
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
FDA	Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IL	Interleukin
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)
PML	Progressive multifocal leukoencephalopathy
PSA	Probabilistic sensitivity analysis
PSI	Psoriasis Symptom Inventory
PSSI	Psoriasis Scalp Severity Index
PSS	Personal social services
PUVA	Psoralen and long-wave ultraviolet radiation
QALY	Quality-adjusted life year
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
Q12W	Every 12 weeks
RCT	Randomised controlled trial
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SIB	Suicidal ideation and behaviour
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SPC	Summary of product characteristics
sPGA	static Physician's Global Assessment
STA	Single Technology Appraisal
TA	Technology Appraisal
TNF	Tumour necrosis factor

1 Summary

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

Brodalumab (Kyntheum®) is a fully human immunoglobulin G2b monoclonal antibody with a high affinity for interleukin (IL)-17 receptor A. It was granted a European marketing authorisation (EU/1/16/1155/001) on 17 July 2017. The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1 and 2, followed by 210 mg every 2 weeks.

The NICE scope reflects the licence; brodalumab is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy. However the company submission (CS) further specifies a population of patients who are candidates for systemic therapy, and for whom standard systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. The evidence review group (ERG) agrees that it is appropriate to address only this more specific population in the submission because in UK clinical practice brodalumab would be used after non-biological systemic therapy in the treatment pathway.

The comparators included in the CS are restricted to tumour necrosis factor (TNF)-alpha inhibitors (etanercept, infliximab and adalimumab), ustekinumab, secukinumab, apremilast, ixekizumab, dimethyl fumarate (DMF) and best supportive care (BSC). The NICE scope also included non-biological systemic treatment and phototherapy, but, reflecting the more specific population, the ERG agrees that the restricted list of comparators is appropriate.

The intervention and outcomes assessed in the submission match those specified in the NICE scope, although specific results relating to psoriasis symptoms on the face and relapse rates are not presented, despite being listed as outcomes to be addressed in the company submission.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company conducted a systematic review to identify evidence on the clinical effectiveness and safety of brodalumab and relevant comparators for the treatment of adult patients with moderate to severe plaque psoriasis.

Three multicentre double-blind randomised controlled trials (RCTs) are described in the submission: AMAGINE-1 compared brodalumab 140 mg every two weeks (Q2W) and brodalumab 210 mg Q2W with placebo; and AMAGINE-2 and AMAGINE-3 both compared brodalumab 140 mg Q2W and brodalumab 210 mg Q2W with placebo and ustekinumab. The AMAGINE-2 and AMAGINE-3 trials were identical in design. All three trials were well conducted. The primary efficacy outcomes were the proportion of patients achieving a Psoriasis Area and Severity Index (PASI) 100 response and/or a PASI 75 response and the proportion of patients achieving a static Physician's Global Assessment (sPGA) response at week 12.

The AMAGINE-1 trial included a 12 week induction phase, followed by a 40 week maintenance or withdrawal and retreatment phase. The AMAGINE-2 and AMAGINE-3 trials included a 12 week induction phase, followed by a 40 week maintenance phase. Patients in all three trials were eligible to enter an open-label extension phase, which was planned to last a further 4 years. However, all three trials were terminated on 22 May 2015, when Amgen announced that it had commenced termination of its participation in the co-development and commercialization of brodalumab with AstraZeneca; the decision was based on events of suicidal ideation and behaviour (SIB) in the brodalumab program, which Amgen believed likely to necessitate restrictive labelling. Therefore, extension phase data are reported at 120 weeks for AMAGINE-1 and AMAGINE-2 and 108 weeks for AMAGINE-3.

The AMAGINE trials demonstrated that brodalumab (210 mg Q2W) significantly reduced the severity of psoriasis and its impact on health related quality of life, compared with placebo: a statistically significant difference was found between brodalumab (210 mg Q2W) and placebo for all of the outcomes reported at 12 weeks, including PASI 100 response (37-44% versus 0.3-1%), PASI 75 response (83-86% versus 3-8%), sPGA score of 0 or 1 (76-80% versus 1-4%), sPGA score of 0 (37-45% versus 0.3-1%), Psoriasis Symptom Inventory (PSI) response (61-68% versus 4-7%), Dermatology Life Quality Index (DLQI) score of 0 or 1 (56-61% versus 5-7%), ≥5-point improvement in DLQI score (84-88% versus 22-31%). In comparison with ustekinumab (AMAGINE-2 and AMAGINE-3 trials), patients taking brodalumab (210 mg Q2W) were statistically significantly more likely to achieve a PASI 100 response (37-44% versus 19-22%), PASI 90 response (69-70% versus 47-48%), sPGA score of 0 or 1 (79-80% versus 57-61%), sPGA score of 0 (37-45% versus 19-22%) and PSI response (61-68% versus 52-55%) at 12 weeks; PASI 75 response rate was significantly higher with brodalumab than ustekinumab in AMAGINE-3 (85% versus 69%), but statistical significance was not reported for AMAGINE-2 (86% versus 70%). The proportion of patients with a DLQI score of 0 or 1 (59-61% versus 44%) or ≥5-point improvement in DLQI score (87-88% versus 83-85%) was numerically higher with brodalumab compared with ustekinumab, although statistical significance was not assessed.

From week 16 of the AMAGINE-2 and AMAGINE-3 trials, patients with an inadequate response to brodalumab or ustekinumab could receive rescue therapy with either brodalumab (210 mg Q2W) or ustekinumab; 46-47% patients randomised to ustekinumab required rescue therapy, compared with 29-30% patients randomised to brodalumab.

In AMAGINE-2 and AMAGINE-3, psoriasis severity was assessed at 52 weeks (the analysis included brodalumab patients who had previously received a lower dose of brodalumab prior to re-randomisation); PASI 75 [redacted], PASI 90 [redacted], PASI 100 [redacted], sPGA (61-63% versus 45-46%) responses and the proportion of patients with

DLQI scores of 0 or 1 [redacted] were numerically higher with brodalumab compared with ustekinumab, although statistical significance was not assessed. For patients who continually received brodalumab (210 mg Q2W), or ustekinumab throughout the study, PASI 75 and PASI 90 response rates at week 12 were maintained to week 52, while PASI 100 response rates increased slightly; however, data are not provided on relapse rates so it is not possible to know if all patients achieving these thresholds at week 12 maintained their response or if some patients stopped responding, while others developed a response only after week 12.

The results of the subgroup analyses demonstrate that brodalumab 210 mg Q2W was significantly more efficacious than placebo and ustekinumab regardless of disease severity or prior exposure to systemic therapy, phototherapy and biological therapy.

Across the three AMAGINE trials withdrawal rates in patients treated with brodalumab were low with around 88% completing the study to week 52; for patients receiving the 210 mg Q2W dose, 81-82% patients completed the study to week 52. The ERG notes this is comparable with the drug survival rates published for other biologics.

During the 12 week induction phase of AMAGINE-2 and AMAGINE-3, the proportion of patients with an adverse event was higher in the brodalumab 210mg Q2W and ustekinumab groups than in the placebo group, as would be expected with a biological therapy. Rates were similar between the brodalumab and ustekinumab groups in the induction phase (59.0% ustekinumab vs 57.8% brodalumab) and maintenance phase. The CS states that in AMAGINE-1 the proportion of patients with adverse events in the induction phase was similar in the brodalumab and placebo groups, although the ERG notes that the data in Table 8 shows that it was higher in the brodalumab group (50.9% placebo vs. 59.0% brodalumab).

Candida infections were more frequent in patients receiving brodalumab 210mg Q2W than in the ustekinumab or placebo groups. It was confirmed by the clinical advisor to the ERG that IL-17 inhibitors cause an increased risk of candida infection. All candida infections were graded as mild or moderate. Incidence and rates of serious adverse events were similar in the brodalumab and ustekinumab groups in AMAGINE-2 and AMAGINE-3.

Some patients in the AMAGINE trials experienced SIB and overall there were four completed suicides, although one was later adjudicated as indeterminate. The CS summarises some of the evidence on the risk of SIB, concluding that the data suggest that the risk of SIB is not higher with brodalumab than with other biological therapies. However the ERG notes that the US Food and Drug Administration (FDA) report on brodalumab and the European public assessment report (EPAR) are

unable to draw firm conclusions on a relationship between brodalumab and SIB. The SPC also includes warnings and precautions on SIB.

Two small phase II RCTs comparing brodalumab with placebo were included in a network meta-analysis (NMA), but not described in the submission. The ERG requested clarification about the exclusion of the additional brodalumab RCTs from the submission, as they met the stated inclusion criteria for the systematic review. In their response the company stated that the submission focussed on describing the larger phase III studies due to space constraints.

Network meta-analysis

A NMA was undertaken in order to compare brodalumab with the other therapies available at the same point in the treatment pathway. The NMA was based on short-term efficacy data from individual trials. The NMA appears to have included all relevant trials of brodalumab and the comparator therapies. Studies were assessed for quality using appropriate criteria and the results of the quality assessment suggest that the risk of bias for most studies was low. Adequate details of the included studies are presented in the submission. The patient characteristics and study design of the trials included in the NMA appear similar enough to be pooled, although the baseline quality of life of patients in the AMAGINE trials was generally slightly poorer than that of patients in many of the other trials, where reported, and the proportion of patients who had received prior biological therapy was slightly higher in the AMAGINE trials than many of the other trials.

The base-case NMA included data from 59 RCTs, which included both licensed doses of the therapies specified in the scope, along with unlicensed doses and conventional systemic therapies. A sensitivity analysis was undertaken which included only licensed doses and dosing regimens currently recommended by NICE (sensitivity analysis 1). This analysis is consistent with NMAs undertaken in other recent NICE Single Technology Appraisals (STAs) of treatments for moderate to severe plaque psoriasis in adults. In response to the ERG's request for additional sensitivity analysis results, the company provided additional results for sensitivity analysis 1, sensitivity analysis 4 (which excluded studies in which more than 30% of randomised patients reported having previously tried biological therapy) and a sensitivity analysis excluding all phase II studies.

When ranked in order of effectiveness (median probability of achieving a PASI 75 response), the results for the base case NMA and sensitivity analyses are consistent: ixekizumab, brodalumab, secukinumab, infliximab, ustekinumab, adalimumab, etanercept, apremilast, DMF, placebo. Similarly, for PASI 50, PASI 90 and PASI 100 response, brodalumab had a higher probability of response than ustekinumab, adalimumab, etanercept, apremilast, DMF and placebo, and a similar probability of response to ixekizumab, secukinumab and infliximab.

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

The evidence for the clinical effectiveness of brodalumab is based on three good quality RCTs and the results are likely to be reliable. All three AMAGINE trials included brodalumab at the licensed dose (210 mg Q2W) in addition to lower doses; only results for the licensed dose were described in detail in the submission. Trial inclusion criteria appear to have been appropriate and baseline characteristics were similar across treatment groups. However, inclusion criteria relating to disease severity were not the same as the threshold specified in the NICE treatment pathway (PASI score ≥10 and DLQI score >10); the AMAGINE trials recruited patients with a higher PASI score (≥12) but did not specify a minimum DLQI score. In addition, 17-35% patients in the AMAGINE trials had not received previous systemic therapy or phototherapy, which is not consistent with the proposed positioning of brodalumab in the treatment pathway. The AMAGINE trials also excluded patients who had previously received ustekinumab or anti-IL-17 therapy, which may not be reflective of how brodalumab would be positioned in practice. Therefore, the results of the AMAGINE trials may not be entirely generalisable to the proposed eligible population.

The NMA was appropriate to pool trial results and compare treatments available for moderate to severe plaque psoriasis. The NMA results presented are the proportion of patients at the end of the study-defined induction period achieving each level of PASI response (PASI 50, PASI 75, PASI 90 and PASI 100) for each treatment, reflecting the economic model. Risk ratios are also presented for each drug compared with placebo and for brodalumab compared with the other treatments. The CS states that other outcomes were either poorly or inconsistently reported across studies and were therefore not prioritised for synthesis. However, the British Association of Dermatologists' (BAD) guidelines for biologic therapy for psoriasis, published in April 2017, also assessed mean change in DLQI score and tolerability in their NMA.

The results of the NMA, in terms of ranking order of effectiveness, were consistent with those of NMAs undertaken in other recent STAs of treatments for moderate to severe plaque psoriasis in adults and the NMA undertaken for the development of the BAD guidelines.

There was considerable variation in PASI response rates in the placebo arms of the trials included in the NMA; PASI 50 response rates ranged from 5.1% to 33.3%. As a means to assess this existing between-study heterogeneity, NMA meta-regression models on baseline risk (i.e. placebo response) were also explored in the company submission. A comparison of unadjusted and adjusted models was reported. In the submission, the selection of the adjusted or the unadjusted synthesis model results to inform the economic model was based on the DIC statistics; the unadjusted model was chosen. However, the ERG considers the placebo adjusted synthesis model to be more appropriate than the unadjusted model despite the marginally higher DIC value. Predicted PASI responses from the

ERG's revised placebo adjusted synthesis model were similar to those presented by the company, providing reassurance regarding the company analyses. The treatment rankings presented by the company were unaltered.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's search identified a single published cost-effectiveness study of brodalumab. The study was undertaken prior to the EU marketing authorisation and assumptions were made in relation to the potential acquisition cost. Given this limitation and issues regarding the generalisability of the setting, the ERG considers the de-novo cost-effectiveness analysis reported in the company submission to be the most relevant source of evidence.

The cost-effectiveness of brodalumab was evaluated using a Markov state-transition model developed in Microsoft Excel. The use of a Markov model was justified based on the need to evaluate treatment sequences over an appropriate time horizon. The model includes a total of nine treatment sequences which include three lines of active therapy, followed by BSC. Brodalumab was 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.

Brodalumab 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, alongside consideration of including different mechanisms of action to the preceding line. Across the majority of sequences, ustekinumab and secukinumab were included as the second and third-line treatments, respectively.

Each line of treatment in a sequence starts with an induction period lasting between 10 and 16 weeks. At the end of the induction period, individuals are assigned to one of five 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≤50 are assumed to discontinue their treatment and then switch to the next treatment in the sequence.

During the maintenance period, individuals are assumed to continue to receive the same treatment and maintain the same PASI response until the treatment is discontinued due to loss of response and/or adverse events. In line with previous economic studies identified by the company, it was assumed that individuals discontinue treatment at the same constant annual rate for all treatments.

Individuals who do not respond to the third line of treatment (or who initially respond but then subsequently discontinue treatment) move to the BSC state with individuals assumed to be treated with non-biologic supportive therapies.

The perspective of the analysis was the NHS and Personal Social Services. An annual discount rate of 3.5% was applied to both costs and health effects, in line with NICE guidance. A time horizon of 40 years was chosen as it was considered sufficient to capture all relevant differences in costs and benefits between comparators.

The measure of treatment effectiveness used in the model was 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 NMA. In the company 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 assumed in the maintenance period for all treatments. This rate included discontinuation for any reason (e.g. loss of response, adverse events, etc). The rate of discontinuation was informed by real world evidence on the long-term drug survival rates from a large UK registry (BADBIR).

Outcomes of the model were expressed using quality adjusted life years (QALYs). The utility values used in the model were derived from EuroQol-5D questionnaire (EQ-5D) -3L data (UK tariffs applied) collected in the AMAGINE-1 trial of brodalumab 210 mg Q2W versus placebo. 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 each PASI response category. The base-case analysis only included EQ-5D-3L data from individuals with a baseline DLQI>10.

The resource use and costs included in the model comprised drug acquisition, administration, monitoring, adverse events and BSC. Unit costs were sourced from relevant UK sources including: 2015/2016 reference costs; Monthly Index of Medical Specialties (MIMS); Personal Social Services Research Unit (PSSRU) and other published literature.

Fully incremental cost-effectiveness ratios (ICERs) and pairwise ICERs for the brodalumab sequence compared to each comparator sequence were reported. In the fully incremental ICER comparison, there were 3 non-dominated (dominance and extended dominance) sequences. Of the non-dominated sequences, the least effective and lowest cost was the sequence starting with DMF. The deterministic ICER of the brodalumab sequence was reported to be £13,353 per QALY compared to the DMF sequence. The ixekizumab sequence was the most effective and most costly of the non-dominated

sequences. The ICER of the ixekizumab sequence versus the brodalumab sequence was £894,010 per QALY.

In the pairwise ICER comparisons, the brodalumab sequence dominated sequences which started with the following treatments: adalimumab; infliximab; secuckinumab and ustekinumab. The ICER of the brodalumab sequence compared to less effective and non-dominated sequences ranged from £7,145 (versus the etanercept sequence) to £13,353 (versus the DMF sequence). The ICER of the more costly and effective ixekizumab sequence was £894,010 per QALY compared to the brodalumab sequence.

The company also presented ICER results from their probabilistic analysis. The ICERs were similar to the deterministic estimates. The company reported that at a threshold of £20,000 per QALY gained, the brodalumab sequence had the highest probability of being cost-effective (96%), followed by the DMF sequence (4%). At a £30,000 threshold, the brodalumab sequence was reported to have a 100% probability of being the most cost-effective.

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

The ERG's critique identified 5 main issues:

(i) The sequences evaluated by the company were restrictive in terms of the number of sequences included and the position of brodalumab 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 ERG proposed minor revisions to the WinBUGs code used for the NMA and stated a clear preference for the placebo-adjustment NMA analysis. The ERG also noted that, in recognising the existing baseline risk heterogeneity of PASI response across included trials, the heterogeneity in baseline risk across the three pivotal phase 3 RCTs for brodalumab needed to be more explicitly considered.

(iii) The ERG considered that the utility regression model used in the company base-case should have been adjusted for baseline EQ-5D. The results from the alternative regression approaches presented by the company showed that the regression model adjusting for baseline EQ-5D consistently performed better in terms of goodness of fit across a range of measures (e.g. AIC, BIC, etc).

(iv) The ERG concluded that an adjustment to the dosing assumptions for brodalumab was appropriate based on the current summary of product characteristics (SPC) wording and the provision of 2-injections within each pack. The ERG also considered that the costs of non-responders and additional monitoring costs for DMF should be included in the base-case.

(v) The ERG noted that there is uncertainty regarding the appropriateness of assuming a constant annual discontinuation rate for all treatments.

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

1.6.1 Strengths

The clinical effectiveness evidence is derived from three good quality RCTs, two of which compared brodalumab with an active comparator, in addition to placebo. A NMA was undertaken in order to compare brodalumab with the other therapies available at the same point in the treatment pathway.

The ERG considered the company's economic model to meet the requirements of the NICE reference case and to be of high-quality generally. The company provided detailed and helpful responses to the ERG's points for clarification. The ERG acknowledges the extensive additional work that the company undertook to respond to their requests.

The company base case and sensitivity analysis scenarios were successfully reproduced by the ERG in deterministic and probabilistic analyses. Basic logical tests performed by the ERG entering extreme values for costs and efficacy and 0-1 values for utility showed the model behaved logically. The ERG conducted its own validation of the VBA code, the Excel functions and linkages between spreadsheets (cell-by-cell validation) that produced the modelling outputs. All the VBA code and linkages were correctly functioning and model inputs were found to match those reported of the submission with one minor exception that had no noticeable impact on the final results.

1.6.2 Weaknesses and areas of uncertainty

An area of uncertainty in the analysis of clinical effectiveness was the placebo response rates. In the AMAGINE trials [redacted]. Across the trials in the NMA placebo rates differed markedly, though the results of the adjusted (for placebo response rate) and unadjusted models were similar. Another area of uncertainty was around SIB, which the ERG note the FDA and EPAR reports were unable to exclude as a risk associated with brodalumab.

Of the main areas of uncertainty identified, 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).

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The key uncertainties identified by the ERG were explored in 12 separate scenarios. At a £20,000 threshold, brodalumab was ranked 1st (i.e. most efficient single treatment) in 11 of the 12 scenarios. At a £30,000 threshold, brodalumab was ranked 1st in 10 of the 12 scenarios explored by the ERG. The only scenarios where brodalumab was ranked lower than 1st was when the ERG explored assumptions that it did not consider more appropriate or necessarily more plausible than the assumptions or scenarios than those included in the company base-case.

An alternative ERG base-case was included which combined changes from 6 of the 12 separate scenarios. The specific scenarios included were those the ERG considered provided more appropriate or plausible assumptions than the company base-case.

The treatment rankings identified in the ERG alternative base-case were identical to those derived from the company base-case model. The ERG concludes that their alternative assumptions had no material effect on the conclusions that can be drawn from the company base-case. Importantly, brodalumab was identified as the most efficient treatment (i.e. the highest rank based on NMB vs BSC alone) in the ERG and company base-case analyses. The ERG considers that this provides significant reassurance and confirmation regarding the robustness of the company's results. However, these results exclude the confidential patient access schemes (PAS) for several comparators (ixekizumab, secukinumab and apremilast). 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 CS includes an appropriate and relevant summary of the underlying health problem.

Psoriasis is a chronic inflammatory, immune-mediated skin disorder, with a relapsing-remitting pattern.[1] The CS states that the prevalence is 3% of the UK population.[2] Around 20% of these patients have moderate to severe disease, which would be around 230,000 people in England.[3] Chronic plaque psoriasis is the most common of five forms of psoriasis, accounting for 90% of all cases.[3] Symptoms can include scaling, itching, redness, tightness of the skin, bleeding and burning, which can affect sleep, physical functioning, activities of daily living and work productivity.[4-9] Comorbidities associated with chronic plaque psoriasis include other autoimmune diseases, hyperlidaemia, hypertension, diabetes and depression.[10, 11] Research has found an increased risk of adverse cardiac events[12] and death in people with severe psoriasis.[13] The CS highlights the impact chronic plaque psoriasis has on quality of life, which can lead to profound psychological morbidity, reduced employment and income and increased risk of depression and anxiety.[1, 11, 14]

2.2 Critique of company's overview of current service provision

Overall the CS provides an appropriate and relevant summary of the current service provision for patients with moderate to severe psoriasis.

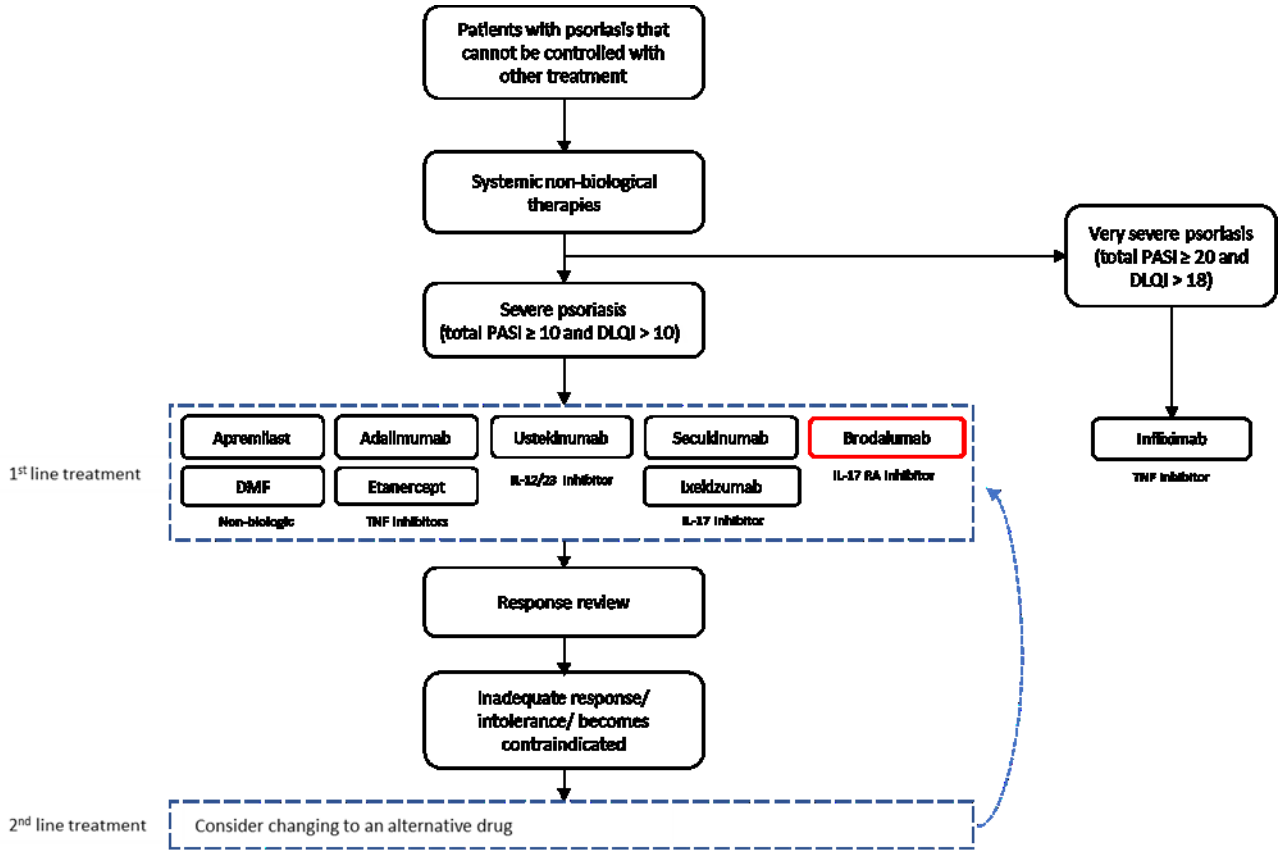
As highlighted in the CS, the NICE pathway for psoriasis specifies topical therapy as a first line treatment.[15] For patients with more severe psoriasis, phototherapy or systemic non-biological treatments are recommended. For adults with severe psoriasis (PASI score ≥ 10 and DLQI score >10) who do not respond to, are intolerant of or have a contraindication to standard systemic therapies and phototherapy, NICE recommends apremilast, DMF or systemic biological therapies.[16, 17]

There are several existing biological therapies available for adults with severe psoriasis, including adalimumab, etanercept, infliximab (for patients with very severe disease; PASI ≥20 and DLQI >18), ustekinumab, secukinumab and ixekizumab.[16] These therapies target different parts of the IL-17-Th17 pathway,[16, 18] which plays a central role in amplifying the immune response in psoriasis patients. The CS states that the majority of patients do not achieve complete skin clearance with the anti-TNF agents (adalimumab, etanercept and infliximab) or the IL-12/-23 inhibitor ustekinumab,[19] and many stop treatment due to loss of response or side effects.[20-22] Studies of secukinumab and ixekizumab, which target IL-17A activity, have shown higher response rates and complete skin clearance in some patients.[16] According to the clinical advisor to the ERG, a key issue with biological therapies is that some patients will only respond to certain drugs. Patients can experience primary failure, with non-response evident within the first few weeks, or secondary failure where the therapy stops being

effective after months or years of treatment.[16] There is therefore a need for a range of treatment options.

The CS states that brodalumab is a fully human monoclonal antibody, which targets the IL-17-receptor-A,[23] with a different mechanism of action to the other IL-17A inhibitors. As can be seen in Figure 1, the CS positions brodalumab in the treatment pathway as an option alongside the other biological therapies (except infliximab which is only recommended for patients with very severe disease). If a patient does not respond adequately to the chosen treatment, physicians should consider switching them to an alternative therapy.[16]

Figure 1: Proposed position of brodalumab within the treatment pathway for patients with moderate to severe psoriasis (From CS, Figure 3, page 20)



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. The decision problem addressed in the CS further specifies a population of patients who are candidates for systemic therapy, and for whom standard systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. The clinical advisor to the ERG confirmed that, although biological therapies such as brodalumab 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. Based on this advice and the proposed positioning of brodalumab in the treatment pathway, the ERG agrees that it is appropriate to address only this more specific population in the submission.

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.[16, 17] 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 trials ranged from [redacted]. 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 is brodalumab at the recommended dose of 210 mg administered by subcutaneous injection at weeks 0, 1 and 2, followed by 210 mg every 2 weeks, which is in line with the NICE scope.

3.3 Comparators

The decision problem addressed in the CS includes the comparators specified by NICE for people with severe or very severe psoriasis for whom standard systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. These are TNF-alpha inhibitors (etanercept, infliximab, adalimumab), ustekinumab, secukinumab, apremilast, ixekizumab, DMF and BSC. The decision problem addressed in the CS does not include systemic non-biologic therapies or phototherapy with ultraviolet radiation, which are included in the NICE scope as comparators for patients in whom non-biologic systemic therapy or phototherapy is suitable. The CS states that the rationale for the difference between the decision problem addressed and that specified in the NICE scope is that, in clinical practice, brodalumab would likely be offered at a similar point in the treatment pathway as other approved biological treatments, apremilast and DMF, after standard systemic therapies have failed, are contraindicated or are not tolerated. The clinical advisor to the

ERG confirmed that this reflects clinical practice in the UK and therefore the ERG considers the company's exclusion of these comparators appropriate.

3.4 Outcomes

The outcomes listed as being addressed in the CS are severity of psoriasis (including PASI), psoriasis symptoms on the face, scalp and nails, mortality, response rate, relapse rate, adverse effects and health-related quality of life (HRQoL). These match the outcomes specified in the NICE scope. They are all addressed in the clinical evidence presented in the CS except for psoriasis symptoms on the face, for which no specific evidence is provided, and relapse rates. Although the maintenance of response rates is assessed in the clinical evidence, data are not presented on numbers of patients who initially responded to treatment and then experienced a relapse. The focus of the submission and NMA is PASI response rates. Primary endpoints in the clinical trials include PASI 75, PASI 100 and sPGA response.

The ERG considers all outcomes to have been measured appropriately. Severity of psoriasis was measured with PASI response rates, PSI response and sPGA response. Health related quality of life was measured with the DLQI, EQ-5D and the Hospital Anxiety and Depression Scale (HADS). Psoriasis symptoms on the nails and scalp were measured by improvement in Nail Psoriasis Severity Index (NAPSI) score and Psoriasis Scalp Severity Index (PSSI) score respectively. Mortality is considered as part of the safety results.

3.5 Other relevant factors

The CS includes analysis of the subgroups specified in the NICE scope (previous use of systemic non-biological therapy, previous use of biological therapy and severity of psoriasis), alongside various other subgroups the company considered relevant.

The CS includes a section on equality considerations, which claims that there are wide variations in how psoriasis is treated in adults in the UK,[24] specifying that older patients are less likely to be treated with biological therapies.[25] The CS states that the appraisal is not anticipated to exclude from consideration any people protected by equality legislation or lead to recommendations that have different or adverse impacts.

The CS gives details of a PAS agreed with the Patient Access Scheme Liaison Unit/Department of Health.

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(s)

The CS describes a systematic review of the clinical effectiveness and safety of brodalumab and relevant comparators (adalimumab, apremilast, DMF, etanercept, infliximab, ixekizumab, secukinumab and usetekinumab) for the treatment of adult patients with moderate to severe plaque psoriasis. It is not clear in the CS whether just one systematic review was undertaken to identify both studies of brodalumab and studies for the NMA, or whether these were separate processes. In response to a request for clarification, the company stated that the eligibility criteria presented in Table 78 and 79 of the CS are for both the systematic literature review (SLR) of brodalumab and the NMA, for which some additional criteria were also used. The CS presents information on searches and selection criteria that refer to brodalumab and all comparators. The company also conducted two systematic reviews of non-RCT evidence on the efficacy and safety of brodalumab, although information on these reviews is only included in the appendix.

4.1.1 Search strategy

The company submission describes the search strategies used to identify relevant RCTs of brodalumab and potential comparator therapies (secukinumab, etanercept, infliximab, adalimumab, ustekinumab, apremilast, ixekizumab, DMF) used for the treatment of moderate to severe plaque psoriasis. The search strategies are presented in Appendix D.1.1 of the submission (pages 177 to 188). The databases searches were carried out on 31st August 2016 and updated on 25th July 2017, with searches for trials of DMF carried out on 8th August 2017. The following databases were searched: MEDLINE, MEDLINE in Process, EMBASE, and the Cochrane Library. A number of conference proceedings were also scanned from 2013 onwards: International Society for Pharmacoeconomics & Outcomes Research (ISPOR); World Congress of Dermatology; and American Academy of Dermatology. The reference lists of other systematic reviews and NMAs were screened to identify any additional publications. The reporting of the searches was clear with sufficient detail to allow the database searches to be reproduced. The ERG notes that the searches of the Cochrane Library included redundant publication type search terms; these are not necessary as the content of this resource is already filtered by publication type.

In addition to the searches for RCTs the company also undertook a series of searches for non-RCT evidence (including retrospective studies, cohort analyses, case control studies, observational studies and long-term extensions) that are reported in Appendix D.1.4 of the submission (pages 247 to 252).

The main company submission does not refer to these non-RCT searches or their results. These database searches were carried out on 31st January 2017 and updated on 15th August 2017. The following databases were searched: MEDLINE, MEDLINE in Process, EMBASE, and the Cochrane Library. The ERG notes that the PRISMA flowchart (page 255) refers to search results from the EconLIT database but the search strategy used is not described along with the other database search strategies. A number of conference proceedings were also scanned from 2014 onwards: International Society for Pharmacoeconomics & Outcomes Research (ISPOR); World Congress of Dermatology; and American Academy of Dermatology. The reporting of the searches was clear with sufficient detail to allow the database searches to be reproduced. The ERG notes that the search of the Cochrane Library that retrieved 0 hits was probably redundant as the individual databases included in this resource focus on systematic reviews, RCTs, and economic evaluations rather than retrospective studies, cohort studies and case studies.

4.1.2 Inclusion criteria

Full eligibility criteria for the review of biologic therapies and apremilast are presented in Table 78 of the submission. RCTs that assessed brodalumab, secukinumab, etanercept, infliximab, adalimumab, ustekinumab, apremilast or ixekizumab in adult patients with moderate to severe chronic plaque psoriasis were included in the review. RCTs that exclusively recruited patients with both psoriasis and psoriatic arthritis were excluded. Comparators in included studies could be any monotherapy, including unlicensed doses of biologic or non-biologic systemic therapies. Non-English language publications were excluded from the review. Separate eligibility criteria are presented for studies of DMF (Table 29 of the submission) but these are similar.

Appropriate methods were used for screening titles and abstracts, with two reviewers screening independently and any disagreements resolved by discussion or a third reviewer. The CS does not specify the methods used for full text screening so it is unclear whether appropriate methods were used to reduce the potential for bias and error at this stage. The exclusion of non-English language publications introduced some potential for bias, although the ERG is not aware of any studies that were missed due to this. A PRISMA flow diagram is included in the appendix but it contains errors and a list of studies excluded from the systematic review is not presented. The company provided a corrected PRISMA flow diagram and a list of studies excluded from the systematic review in response to a request for clarification. Two phase II RCTs[26, 27] identified through the SLR met the inclusion criteria but were not described in detail in the submission, despite being included in the NMA. In response to a request for clarification, the company explained that the submission focused on the larger phase III studies due to space constraints. The ERG considers it appropriate that these trials were not described in detail given their small size and the availability of the larger, longer-term,

active-controlled AMAGINE-2 and AMAGINE-3 trials. However, justification should have been provided in the CS for excluding them.

4.1.3 Data extraction

Data were extracted from each included study on trial design, inclusion criteria, study population characteristics, interventions, outcomes measures, length of follow-up and the proportion of patients achieving PASI 50, PASI 75, PASI 90 and PASI 100 response criteria. Additional data were extracted for the AMAGINE trials. No information is given on how many reviewers undertook data extraction so it is not clear if appropriate methods were used to reduce potential for bias and error. The ERG considers there to be sufficient data from the three AMAGINE trials presented in the submission. However only limited data are presented on two phase II trials of brodalumab[26, 27] identified through the systematic review and included in the NMA. The appendix includes brief summaries of three open label extension studies of brodalumab that were identified through the systematic review of non-RCT evidence, but this information is not presented in the main submission.

4.1.4 Quality assessment

Quality of the trials was assessed using the concise critical appraisal checklist provided by NICE in the STA user guide.[28] The checklist covered randomisation, concealment of treatment allocation, similarity of baseline characteristics, blinding, imbalances in drop-outs, completeness of outcome reporting and intention-to-treat analysis. Results of quality assessment of the AMAGINE trials are presented in Table 12 of the submission, and detail given in Table 86 in Appendix D. Results of quality assessment of the trials included in the NMA are presented in Table 87 of the submission. Overall the three AMAGINE trials are judged to be of high quality with low risk of bias. Sufficient detail is given on most domains but no information is provided on concealment of treatment allocation as the text in this section instead addresses the blinding of patients and investigators. However as randomisation was by interactive voice response system in AMAGINE-1, concealment of treatment allocation is likely to have been adequate. The clinical study reports (CSRs) confirm that an interactive voice response system was also used in AMAGINE-2 and AMAGINE-3.[29, 30] No information is given on how many reviewers undertook quality assessment.

4.1.5 Evidence synthesis

Results of the three AMAGINE trials are presented separately. No pooled analysis of the three trials is presented in the main submission. Subgroup analyses, presented in Appendix E, use a pooled patient population, of all three trials for brodalumab vs placebo and of AMAGINE-2 and AMAGINE-3 for brodalumab vs ustekinumab. The pooled analysis results involved adding together results from the three trials as if they were from the same trial, rather than calculating a weighted average of the trials. The ERG considers that AMAGINE-1 was not sufficiently similar to AMAGINE-2 and AMAGINE-3 to pool results, given differences in patient characteristics and study design. However, since

AMAGINE-2 and AMAGINE-3 were identical trials, the ERG considers that it would have been appropriate to pool results and it is not clear why a pooled analysis of efficacy in all patients in the AMAGINE-2 and AMAGINE-3 trials was not provided.

A network meta-analysis (NMA) was undertaken to compare brodalumab with the comparator treatments, described in section 4.3 of this report.

4.1.6 Conclusions from critique of systematic review methods

Overall the systematic review conducted is of reasonably high quality. Search strategies appeared appropriate and the ERG does not have concerns that any studies were missed. Appropriate methods were used to limit bias and error in screening titles and abstracts, but information on this is not provided for full text screening, data extraction and quality assessment. Inclusion criteria were appropriate and sufficient data were extracted and presented in the submission. Appropriate quality assessment was undertaken, but concealment of treatment allocation was not fully assessed. Data from the three trials were pooled for subgroup analyses, which the ERG considers appropriate given the similarities. For the main clinical effectiveness section, data are presented separately.

4.1.7 Ongoing studies

The open-label extension phase of the AMAGINE trials was terminated in 2015. The CS states that there are no completed or ongoing studies of brodalumab that will provide additional evidence within the next 12 months.

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

4.2.1 Trials included in the review

Three phase III RCTs of brodalumab are included in the review: AMAGINE-1 (NCT01708590), AMAGINE-2 (NCT01708603) and AMAGINE-3 (NCT01708629). All three studies included at least two different doses of brodalumab, including 210mg Q2W. As other doses are outside the proposed label, the submission focusses on brodalumab 210mg Q2W data. Patients from the three trials were eligible for an open-label extension phase and data from this are also described in the CS.

The CS mentions two phase II studies[26, 27] that were identified through the systematic review but not described in the submission (although both are included in the NMA). In response to a request for clarification, the company explained that the submission focused on the larger phase III studies due to space constraints.

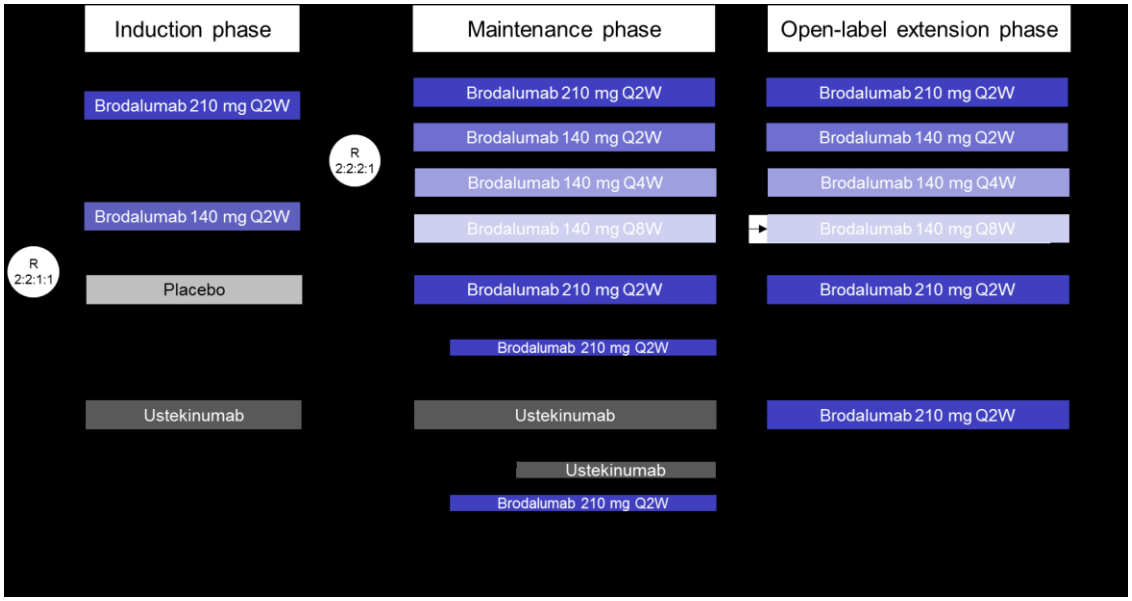
AMAGINE-2 and AMAGINE-3 are the primary focus of the clinical effectiveness evidence in the CS and were identical, multicentre, international RCTs which compared brodalumab with an active

control of ustekinumab and with placebo. Supporting evidence is provided from AMAGINE-1, a multicentre, international RCT that compared brodalumab with placebo.

AMAGINE-2 and AMAGINE-3

The identical AMAGINE-2 and AMAGINE-3 trials were conducted at 142 sites in Australia, Canada, Europe and the USA.[31] Figure 22 shows the study design. Patients were randomised in a 2:2:1:1 ratio to receive brodalumab at a dose of 210mg Q2W or 140mg Q2W, ustekinumab or placebo. At the end of a 12 week induction phase, patients originally randomised to receive brodalumab were re-randomised in a 2:2:2:1 ratio to receive brodalumab 210mg Q2W, brodalumab 140mg Q2W, brodalumab 140mg every 4 weeks (Q4W) or brodalumab 140mg every 8 weeks (Q8W). Those patients randomised to ustekinumab continued to receive the same dose. Patients randomised to placebo began receiving brodalumab 210mg Q2W. Blinding was maintained throughout the 40 week maintenance phase. At the end of the maintenance phase, at week 52, patients receiving ustekinumab were switched to treatment with brodalumab 210mg Q2W for the open-label extension phase. Those already receiving brodalumab continued to receive it at the same dose. From week 16, patients with an inadequate response (single sPGA score ≥ 3 or persistent sPGA scores ≥ 2 over at least a four week period) received rescue treatment. Brodalumab groups received rescue treatment with brodalumab 210mg Q2W. The ustekimumab group received rescue treatment with brodalumab 210mg Q2W at week 16 or ustekinumab if initiating rescue treatment after week 16.

Figure 2: Study design of AMAGINE-2 and AMAGINE-3 RCTs (from CS, Figure 4, page 27, source: Lebwohl et al. 2015[31])

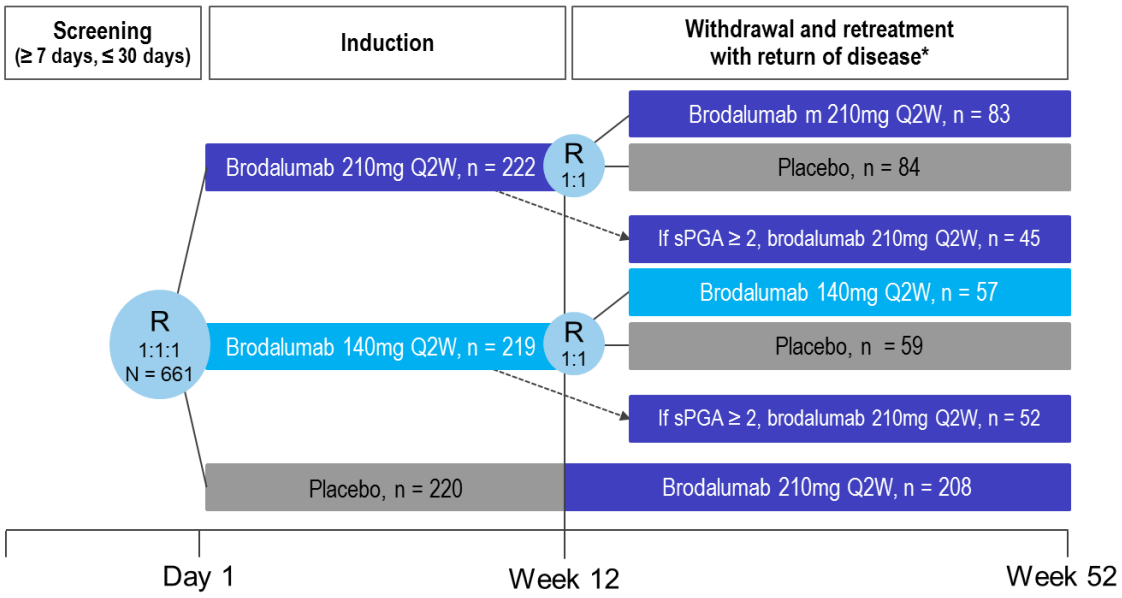


R, randomisation; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks.

AMAGINE-1

AMAGINE-1 was conducted at 73 sites in Canada, Europe and the USA.[32] Patients were randomised in a 1:1:1 ratio to receive brodalumab 140mg Q2W, brodalumab 210mg Q2W or placebo. After a 12 week induction phase, patients originally randomised to one of the brodalumab arms who had an sPGA response (sPGA 0 or 1) were re-randomised 1:1 to their induction dose of brodalumab or to placebo (withdrawal phase). Patients originally randomised to placebo or patients randomised to brodalumab who did not have an sPGA response (sPGA ≥2) received brodalumab 210mg Q2W during the 40 week withdrawal and re-treatment phase. Patients in the withdrawal phase who experienced a return of disease (sPGA ≥3) between 16 weeks and 52 weeks were re-treated with their original dose of brodalumab. At week 52, at the end of the withdrawal and retreatment phase, patients receiving brodalumab continued to receive it at the same dose for the open-label extension phase. 3 shows the study design of AMAGINE-1.

Figure 3: Study design of AMAGINE-1 (from CS, Figure 5, pg 28)



R, randomisation; Q2W, every 2 weeks; sPGA static Physician's Global Assessment.

Open-label extension phase

Patients from all three trials were eligible for an uncontrolled, open-label extension phase which was planned to last for a further four years. The extension phase was stopped on 22nd May 2015, so extension phase data are available for 120 weeks for AMAGINE-1 and AMAGINE-2 and for 108 weeks for AMAGINE-3.

4.2.1.2 Study endpoints

Efficacy assessments were conducted throughout the studies, with key assessments at week 12 and week 52. In AMAGINE-2 and AMAGINE-3, the primary endpoint for comparing brodalumab with ustekinumab was the proportion of patients achieving PASI 100 at week 12. To compare brodalumab with placebo, primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving an sPGA response (clear [0] or almost clear [1]) at week 12. These endpoints were also used in AMAGINE-1 to compare brodalumab with placebo. In general, the ERG consideres these endpoints and outcome measures to be appropriate.

4.2.1.3 Trial populations

The eligible population for all three trials was adults aged 18 to 75 who were candidates for biological therapy for stable moderate to severe plaque psoriasis of at least 6 months' duration. Patients had to have a PASI score ≥ 12, an sPGA score ≥ 3 and involvement of ≥ 10% of the body surface area. Enrolment of patients with previous use of biologic agents was capped at 50% of each study population. Exclusion criteria included medical conditions that could prevent patients from completing the study or interfere with the interpretation of results, for example a known history of tuberculosis or Crohn's disease. Patients using other psoriasis therapies were excluded unless they had completed specified washout periods before the first dose. Full inclusion and exclusion criteria are listed in Table 4 of the submission.

Overall the criteria appear appropriate but there are a few criteria which may influence the extent to which the trials are generalisable to the proposed population in England. For example, the inclusion criteria on disease severity are not the same as the threshold specified in the NICE pathway to be considered for other biological therapies, apremilast and DMF (PASI score ≥ 10 and DLQI > 10)[16, 17]. The AMAGINE trials recruited a population with higher PASI scores (≥ 12) but did not specify a minimum DLQI score. Mean baseline DLQI scores for the different treatment groups across the trials ranged from [redacted]. It is likely that there were patients included with DLQI scores below the threshold specified by NICE.

The clinical advisor to the ERG advised that older patients are often more ill than the general psoriasis population, so the exclusion of patients aged over 75 may have an impact on the generalisability of the trial results to the population seen in practice. Likewise, including only patients with stable psoriasis, who had not had a significant flare of disease for at least six months, may not reflect the severity of psoriasis in the population eligible for brodalumab. The AMAGINE trials excluded patients that had previously received ustekinumab or anti-IL-17 therapy. Excluding patients treated with these commonly-used biological therapies is not reflective of UK clinical practice. In the AMAGINE-1 trial 46% of patients in the placebo arm and 47% in the brodalumab 210mg Q2W arm had received previous biological therapy. This was a lot higher than in the AMAGINE-2 and

AMAGINE-3 trials where previous biological therapy use in the placebo, ustekinumab and brodalumab 210mg Q2W arms ranged from 24% to 29%. This difference suggests that patients in AMAGINE-1 may have had disease that is less responsive to treatment, which may explain the lower placebo response rate seen in AMAGINE-1 compared with AMAGINE-2 and AMAGINE-3.

Baseline characteristics of the three AMAGINE studies are shown in Table 1, excluding those patients randomised to receive brodalumab 140mg Q2W. Overall numbers of patients randomised in each study were 1831 in AMAGINE-2, 1881 in AMAGINE-3 and 661 in AMAGINE-1. Excluding patients randomised to receive brodalumab at a dose of 140 mg Q2W, patient numbers were 1221 in AMAGINE-2, 1252 in AMAGINE-3 and 442 in AMAGINE-1. Baseline characteristics do not show any concerning imbalance across treatment groups. In response to a point for clarification, the company confirmed that no UK patients were included in the AMAGINE trials.

Across the treatment arms in Table 1, 17-35% of patients had not received previous systemic therapy (including non-biologic) or phototherapy. In the proposed pathway, patients eligible for brodalumab in the NHS would be those in whom systemic therapy or phototherapy were ineffective, not tolerated or contraindicated. Psoriasis in this population may be less responsive to treatment than the population in the trials. The clinical advisor to the ERG suggested that different treatment sequencing or drug availability in the countries the trials were conducted in would likely mean the population was not wholly representative of that in the UK.

Overall, the ERG does not have significant concerns about the trial populations but there are some limits to how generalizable they are to the proposed eligible population in the NHS. Patients eligible for brodalumab in NHS practice may have more severe or difficult to treat psoriasis so the efficacy of brodalumab seen in the trials may be higher than would be observed in clinical practice.

Table 1: Demographics and baseline clinical characteristics of patients in the AMAGINE studies (FAS) (from CS, Table 10, page 38)

	AMAGINE-2			AMAGINE-3			AMAGINE-1	
	Placebo (N = 309)	**Ustekinumab (N = 300)**	**Brodalumab 210 mg Q2W (N = 612)**	**Placebo (N = 315)**	**Ustekinumab (N = 313)**	**Brodalumab 210 mg Q2W (N = 624)**	**Placebo (N = 220)**	**Brodalumab 210 mg Q2W (N = 222)**
Mean age, years ± SD	44 ± 13	45 ± 13	45 ± 13	44 ± 13	45 ± 13	45 ± 13	47 ± 13	46 ± 12
Sex, n (%) men	219 (71)	205 (68)	421 (69)	208 (66)	212 (68)	431 (69)	161 (73)	161 (73)
Race, n (%) white [a]	273 (88)	271 (90)	551 (90)	294 (93)	280 (90)	565 (91)	202 (92)	203 (91)
Mean weight, kg ± SD	92 ± 23	91 ± 24	91 ± 23	89 ± 22	90 ± 22	90 ± 23	90.4 ± 20.1	91.4 ± 23.4
Mean body mass index ± SD [b]	30.5 ± 7.0	30.6 ± 7.1	30.5 ± 7.2	29.9 ± 6.7	30.4 ± 6.8	30.3 ± 7.3	30.3 ± 6.6	31.0 ± 7.7
Mean duration of psoriasis, years ± SD	18 ± 12	19 ± 13	19 ± 12	18 ± 12	18 ± 12	18 ± 12	21 ± 12	20 ± 13
Psoriatic arthritis, n (%)	51 (17)	50 (17)	114 (19)	59 (19)	64 (20)	127 (20)	63 (29)	58 (26)
Mean body surface area involved, % ± SD	28 ± 17	27 ± 19	26 ± 16	28 ± 17	28 ± 18	28 ± 18	26.9 ± 17.1	25.1 ± 15.3
Mean PASI score ± SD [c]	20.4 ± 8.2	20.0 ± 8.4	20.3 ± 8.3	20.1 ± 8.7	20.1 ± 8.4	20.4 ± 8.3	19.7 ± 7.7	19.4 ± 6.6
sPGA — n (%) [d]								
3 (moderate disease)	167 (54)	153 (51)	316 (52)	192 (61)	192 (61)	373 (60)	114 (52)	121 (55)
4	120 (39)	132 (44)	254 (42)	113 (36)	103 (33)	226 (36)	91 (41)	87 (39)
5 (very severe)	22 (7)	15 (5)	42 (7)	10 (3)	18 (6)	25 (4)	15 (7)	14 (6)
Mean PSI score ± SD [e]	18.6 ± 7.1	18.9 ± 7.0	18.6 ± 6.8	19.0 ± 6.7	18.7 ± 6.8	18.7 ± 7.2	19.0 ± 6.7	18.9 ± 6.7
Mean DLQI score ± SD [f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous systemic treatment or phototherapy, n (%)	230 (74)	225 (75)	469 (77)	206 (65)	220 (70)	422 (68)	182 (83)	179 (81)
Previous biological therapy, n (%)	90 (29)	84 (28)	177 (29)	76 (24)	75 (24)	157 (25)	101 (46)	105 (47)

[a] Race was self-reported.
[b] The body mass index is the weight in kilograms divided by the square of the height in metres.
[c] PASI scores range from 0 to 72, with higher scores indicating more severe disease.
[d] sPGA scores range from 0 (clear) to 5 (very severe); a score of 3 indicates moderate disease.
[e] PSI scores range from 0 to 32, with higher scores indicating more severe disease.
[f] DLQI scores range from 0 to 30, with higher scores indicating worse HRQoL.
DLQI, Dermatology Life Quality Index; FAS, full analysis set; HRQoL, health-related quality of life; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; SD, standard deviation; sPGA, static physician global assessment; Q2W, every 2 weeks.
Source: Lebwohl et al. 2015[31]; Papp et al. 2016[32]; AMAGINE-1 CSR[33]; AMAGINE-2 CSR[29]; AMAGINE-3 CSR[34]

4.2.2 Summary of the quality of the included trials

Results of the quality assessment are presented in the main submission (Table 12), with more detailed rationale for decisions in Appendix D (Table 86). All trials were large double-blind RCTs with placebo and/or active controls. Based on the information available, randomisation appears adequate in all three trials. For AMAGINE-2 and AMAGINE-3, initial randomisation lists were generated using a permuted block design stratified by baseline body weight, geographic region and previous use of biologic agents. Patients in AMAGINE-1 were randomised by an interactive voice response system, stratified by baseline body weight, geographic region and previous use of biological agents. Re-randomisation at week 12 was stratified by week 12 body weight, induction regimen and week 12 response (sPGA 0 vs sPGA ≥1) in all three trials. The information provided in the CS on concealment of treatment allocation actually refers to blinding of participants and investigators. However, in AMAGINE-1, the use of an interactive voice response system means that treatment allocation concealment is likely to have been adequate. The CS states only that randomisation lists were used in AMAGINE-2 and AMAGINE-3 but the CSRs for these studies confirm that patients were randomised using an interactive voice response system.[29, 30]

Blinding of patients, investigators and the clinical study team was maintained until the end of the maintenance phase. Patients in AMAGINE-2 and AMAGINE-3 received placebo injections where necessary to maintain blinding. For example, patients randomised to brodalumab 140mg received one brodalumab and one placebo injection to mirror the two injections given to the brodalumab 210mg arm. Patients receiving ustekinumab every 12 weeks in the maintenance phase were given placebo injections every two weeks. Rescue treatment was also blinded throughout the maintenance phase. Patients in AMAGINE-1 also received placebo as necessary to maintain the blinding. Further details in the CSR for AMAGINE-1[33] confirm that this was similar to the other trials. After week 28 in AMAGINE-2 and AMAGINE-3 and week 24 in AMAGINE-1, patients were able to self-administer treatment by subcutaneous injection. Although it is not specified in the CS whether this applied to all treatment arms, the CSR for AMAGINE-2 states that all usetekinumab injections were given by qualified staff members.[29] This introduces a potential risk of bias as patients and investigators may have been able to distinguish treatment allocation between brodalumab and ustekinumab.

There is no evidence that any additional outcomes were measured and not reported. Baseline characteristics and numbers of discontinuations were broadly similar across treatment groups. Intention-to-treat analysis, with non-responder imputation (NRI) for missing data, was used for most analyses. In response to a request for clarification, the company provided data on the number of missing values for key endpoints. A similar proportion of patients had missing data across treatment groups at week 12. For PASI and sPGA, outcomes data were missing for between 3-5% patients across treatment groups and there were slightly higher proportions of missing data for PSI (8-11%).

At week 52 PASI and sPGA data were missing for 33% of patients receiving constant brodalumab (210 mg Q2W) in AMAGINE-2 and 35% in AMAGINE-3. Data were missing for a higher proportion of patients treated with ustekinumab (50%) but data for patients who received rescue treatment or treatment change on ustekinumab due to non-response were considered as missing in the data presented. The ERG considers NRI to be an appropriate method for dealing with missing data in this context.

The long-term extension phase of the trial was not controlled and blinding was not maintained for this phase. The analyses of long-term extension phase data used observed data with no imputation. However these data are not referred to extensively or interpreted inappropriately in the CS.

Overall, the ERG considers the three AMAGINE trials to be well conducted with a low risk of bias.

4.2.3 Summary of the results of the included trials

4.2.3.1 Efficacy results

Table 2 shows results for the key efficacy endpoints in the three AMAGINE trials at week 12. All results discussed below refer to brodalumab at the licensed dose of 210mg Q2W only (unless specified otherwise).

Table 2: Clinical responses and patient-reported outcomes at week 12 in the AMAGINE trials (FAS NRI) (from CS, Table 13, page 44)

	AMAGINE-2			AMAGINE-3			AMAGINE-1	
Outcome	**Placebo (N = 309)**	**Ustekinumab (N = 300)**	**Brodalumab 210 mg Q2W (N = 612)**	**Placebo (N = 315)**	**Ustekinumab (N = 313)**	**Brodalumab 210 mg Q2W (N = 624)**	**Placebo (N = 220)**	**Brodalumab 210 mg Q2W (N = 222)**
PASI 100, n	2	65	272	1	58	229	1	93
% (95% CI)	1 (0–2)	22 (17–27)	44 (41–49)	0.3 (0–2)	19 (14–23)	37 (33–41)	0.5 (0–3)	42 (35–49)
p value vs placebo [a]	—	—	< 0.001	—	—	< 0.001	—	< 0.001
p value vs ustekinumab[a]	—	—	**< 0.001** [b]	—	—	**< 0.001** [b]	—	—
PASI 75, n	25	210	528	19	217	531	6	185
% (95% CI)	8 (5–12)	70 (65–75)	86 (83–89)	6 (4–9)	69 (64–74)	85 (82–88)	3 (1–6)	83 (78–88)
p value vs placebo [a,c]	—	—	**< 0.001**	—	—	**< 0.001**	—	**< 0.001** [c]
p value vs ustekinumab	—	—	NT [a]	—	—	0.007 [a]	—	—
sPGA score of 0 or 1, n	12	183	481	13	179	497	3	168
% (95% CI)	4 (2–7)	61 (55–67)	79 (75–82)	4 (2–7)	57 (52–63)	80 (76–83)	1 (0–4)	76 (70–81)
p value vs placebo [a,c]	—	—	**< 0.001**	—	—	**< 0.001**	—	**< 0.001** [c]
p value vs ustekinumab	—	—	< 0.001	—	—	< 0.001	—	—
sPGA score of 0, n	2	65	274	1	58	229	1	93
% (95% CI)	1 (0–2)	22 (17–27)	45 (41–49)	0.3 (0–2)	19 (14–23)	37 (33–41)	0.5 (0–3)	42 (35–49)
p value vs placebo [a]	—	—	< 0.001	—	—	< 0.001	—	< 0.001
p value vs ustekinumab	—	—	< 0.001	—	—	< 0.001	—	—
PSI response, n [d]	21	166	414	20	162	382	9	135
% (95% CI)	7 (4–10)	55 (50–61)	68 (64–71)	6 (4–10)	52 (46–57)	61 (57–65)	4 (2–8)	61 (54–67)
p value vs placebo [a]	—	—	< 0.001	—	—	< 0.001	—	< 0.001
p value vs ustekinumab	—	—	< 0.001	—	—	< 0.001	—	—

Missing data were imputed as nonresponses (see section B.2.4.4 of CS). *p* values for primary endpoints are shown in bold.

PASI 75 and PASI 100 responses indicate reductions from baseline in the PASI score of 75% or more and 100%, respectively. N values are the numbers of patients who were randomly assigned to a study regimen and had a valid measurement value at week 12, after imputation. All *p* values were nominal except as noted otherwise. *p* values were not calculated for the comparison of brodalumab and ustekinumab for the PSI response definition.

[a] *p* values were calculated by means of Bonferroni-based recycling testing (see section B.2.4.3 of CS), which includes all primary and key secondary end point comparisons with placebo and ustekinumab, at a significance level of 0.05.

[b] The *p* value is for the primary end point in the comparison of brodalumab with ustekinumab.

[c] *p* values in this row are for the co-primary endpoints in the comparison of brodalumab with placebo.

[d] A PSI response was defined as a total score of up to 8, with no item having a score greater than 1.

CI, confidence interval; FAS, full analysis set; NRI, non-responder imputation; NT, not tested; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; Q2W, every 2 weeks; sPGA, static physician global assessment.

Source: Lebwohl *et al*. 2015[31]; Papp *et al.* 2016[32]; AMAGINE-1 CSR[33].

AMAGINE-2 & AMAGINE-3

Psoriasis severity at week 12

As shown in Table 2 (Table 13 of the CS), in AMAGINE-2 and AMAGINE-3, brodalumab showed statistically significant greater efficacy than placebo in all specified primary and key secondary endpoints.[31, 32] This was also the case for all primary endpoints comparing brodalumab with ustekinumab, and with all key secondary endpoints in AMAGINE-3.[31] However, the difference in PASI 75 response between brodalumab and ustekinumab was reported as not statistically significant at week 12 in AMAGINE-2, as reported in the publication (P=0.08; based on 'sequence testing', in which the prior endpoint in the sequence was not statistically significant),[31] although this was stated as NT (not tested) in Table 13 of the CS and reported as statistically significant in the text on page 47 of the CS (based on the nominal p-value). In AMAGINE-2, 44% (95% CI 41-49) of brodalumab patients achieved PASI 100 at week 12, compared with 22% (95% CI 17-27) in the ustekinumab group (p< 0.001).[31] In AMAGINE-3, 37% (95% CI 33-41) of brodalumab patients achieved PASI 100 at week 12, compared with 19% (95% CI 14-23) in the ustekinumab group (p< 0.001). PASI 100 responses were achieved by significantly more patients treated with brodalumab than ustekinumab by week 4 of both AMAGINE-2 and AMAGINE-3 [redacted].[29, 30]

There were also significantly more patients achieving PASI 90 with brodalumab (AMAGINE-2: 70.3%; AMAGINE-3: 68.8%) than with ustekinumab (AMAGINE-2: 47.0%; AMAGINE-3: 47.6%) at week 12 (p <0.001).[31] A significant difference was seen as early as week 2 in PASI 90 response. Median time to PASI 90 response was [redacted] for brodalumab and [redacted] for ustekinumab in AMAGINE-2. It was [redacted] for brodalumab and [redacted] for ustekinumab in AMAGINE-3.[29, 30] PASI 75 response rates were significantly higher with brodalumab than with ustekinumab by week 1 [redacted].[29-31] The median time to PASI 75 was 4.1 weeks with brodalumab and 8.1 weeks with ustekinumab in both trials (p <0.001).[31]

Significantly more patients achieved an sPGA response (clear or almost clear) at week 12 with brodalumab than with ustekinumab (p <0.001 in both trials).[31] There was also a statistically significant difference in the proportion of patients achieving clear skin (sPGA 0) at week 12 (p <0.001) and the proportion of patients with a PSI response.[31] In terms of nail

psoriasis, [redacted]. [29, 30]

Rescue therapy at week 16

From week 16, patients who did not have an adequate response to brodalumab (including at doses other than 210mg Q2W) or ustekinumab received rescue therapy, with either brodalumab 210mg Q2W or ustekinumab. Of those patients randomised to ustekinumab for the maintenance phase, 46% in AMAGINE-2 and 47% in AMAGINE-3 received rescue therapy.[31] A lower proportion of patients receiving brodalumab 210mg Q2W received rescue therapy due to inadequate response (AMAGINE-2: 30%, AMAGINE-3: 29%).[31]

Psoriasis severity at week 52

Table 3 shows PASI response rates in AMAGINE-2 and AMAGINE-3 at week 52. According to the CS, [redacted], [29, 30] although the CS does not give p values. PASI 100 and PASI 90 response rates are higher in these data than at week 12, while PASI 75 response rates are lower in both the brodalumab and ustekinumab groups.

Table 3: PASI responses at week 52 in AMAGINE-2 and AMAGINE-3 (EAS, NRI) (from CS, Table 17, page 52)

	AMAGINE-2		AMAGINE-3	
Outcome	**Ustekinumab (not re-randomised) (N = 289)**	**Brodalumab 210 mg Q2W (re-randomised) (N = 334)**	**Ustekinumab (not re-randomised) (N = 301)**	**Brodalumab 210 mg Q2W (re-randomised) (N = 342)**
PASI 100, n % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90, n % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75, n % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Missing data were imputed as nonresponses (see section B.2.4.4 of CS). Patients in all treatment groups with an inadequate response at or before week 52 were imputed as non-responders.
PASI 75, PASI 90 and PASI 100 responses indicate reductions from baseline in the PASI score of ≥ 75%, ≥ 90% and 100%, respectively.
Brodalumab 210 mg Q2W group includes patients initially randomised to placebo or brodalumab 140 mg Q2W and re-randomised to brodalumab 210 mg Q2W.
CI, confidence interval; EAS, efficacy analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks. Source: AMAGINE-2 CSR[29]; AMAGINE-3 CSR[30].

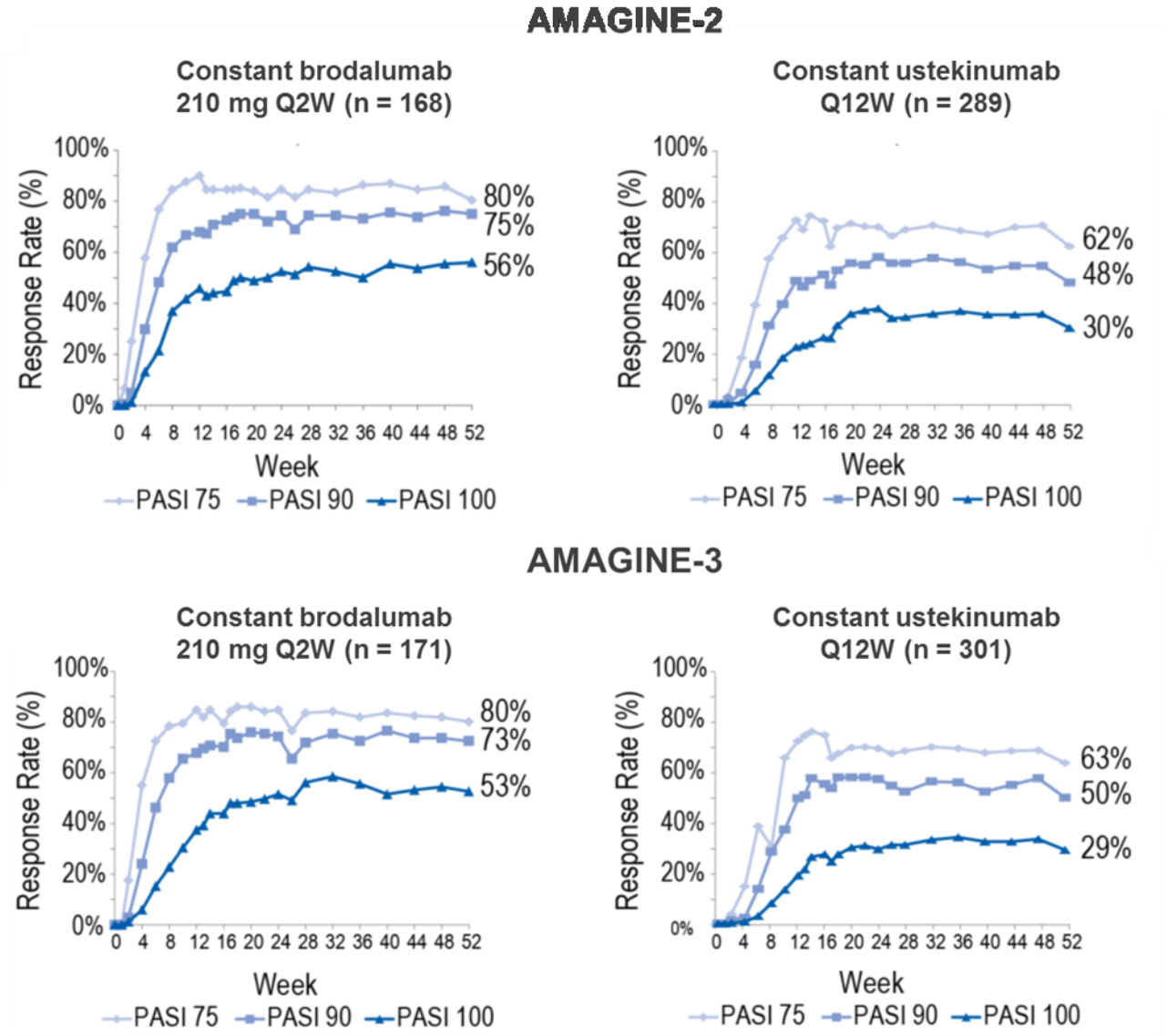
The predefined maintenance endpoint in AMAGINE-2 and AMAGINE-3 was the proportion of patients achieving an sPGA response at week 52. According to the CS, significantly more patients achieved an sPGA response at week 52 with brodalumab than ustekinumab, although p values are not provided. In AMAGINE-2, 62.6% (95% CI 57.1-67.8) of brodalumab patients had an sPGA response at week 52 compared to [redacted] of

ustekinumab patients. In AMAGINE-3, 60.8% (95% CI 55.4-60.0) achieved an sPGA response with brodalumab at week 52 compared to [redacted] with ustekinumab.[29, 30]

As with PASI 75 response rates, these proportions at week 52 are lower than the sPGA response at week 12 for both the brodalumab and ustekinumab arms (shown in Table 2). Therefore while more patients achieved complete clearance or 90% improvement in their psoriasis at week 52, less patients were reaching lower response thresholds with brodalumab or ustekinumab at week 52 than at week 12. However, these analyses are based on the efficacy analysis set (EAS) which included only patients that were re-randomised to brodalumab 210mg Q2W at week 12 (AMAGINE-2 n= 334; AMAGINE-3 n=342), including those who had been receiving brodalumab 140mg Q2W when week 12 measurements were taken. Therefore this cohort differs from the one at week 12 and results provide limited information on maintenance of response. Additionally, by week 52 many patients had withdrawn from the studies and were imputed as non-responders. According to information provided by the company, some of these patients had withdrawn due to lack of response to treatment (see Withdrawals section).

The CS also presents results on maintenance of PASI response at week 52, based on just those patients that received constant brodalumab 210mg Q2W (n=189 in AMAGINE-2 and n=194 in AMAGINE-3) or constant ustekinumab (n=245 in AMAGINE-2 and n=244 in AMAGINE-3) therapy throughout the induction and maintenance phases (shown in Figure 4). The numbers of patients included in the graphs in Figure 4 are slightly lower than they should be based on the numbers stated in the text as receiving constant brodalumab and ustekinumab and it is not clear why there is this inconsistency. Unlike the numbers in the text, the graphs include those on ustekinumab that rescued to brodalumab at week 12, but when this is taken into account the numbers are slightly lower than what would be expected. For patients on brodalumab, PASI 75 and PASI 90 response rates at week 12 were maintained to week 52, with slight increases in PASI 100 response rates at week 52 compared with week 12. Similar results were also seen for those receiving constant ustekinumab therapy.[31] Data is not provided on relapse rates so it is not possible to know if all patients achieving these thresholds at week 12 maintained their response or if some patients stopped responding, while others developed a response only after week 12.

Figure 4: PASI 75, PASI 90, and PASI 100 response rates over time to week 52 (EAS patients receiving constant brodalumab 210 mg Q2W or ustekinumab, NRI) (from CS, Figure 14, page 53)



Missing values were imputed as nonresponses (see section B.2.4.4 of CS). Patients who qualified for protocol-specified treatment change due to rescue prior to week 52 were imputed as non-responders (including patients in the constant ustekinumab group who rescued with brodalumab at week 16). EAS, efficacy analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q12W, every 12 weeks. Source: Lebwohl et al. 2015[31]

Response in patients switching to brodalumab

Table 4 shows outcomes at week 52 in patients that switched to receive brodalumab 210mg Q2W during the AMAGINE-2 and AMAGINE-3 trials.[31] This includes patients randomised to ustekinumab who received rescue therapy with brodalumab from week 16 and patients receiving placebo during the induction phase who switched to brodalumab at week 12. The data presented in this table are based on an 'as observed' analysis with no imputation for missing data. Data on PASI 75 and PASI 100 response and sPGA were available for around

80-87% patients who switched to brodalumab. Over 90% of patients for whom data were available achieved PASI 75 after switching from placebo and over 60% achieved PASI 100 in both trials. A large proportion of those switching from ustekinumab also achieved PASI 75 (91% in AMAGINE-2 and 82% in AMAGINE-3), although less than half achieved PASI 100.[31] As this is based on an 'as observed' analysis, it is difficult to compare response rates with the total population receiving brodalumab 210mg Q2W in the two trials. However the data do suggest that, while proportions of patients achieving a response to brodalumab were broadly similar in those switching from ustekinumab or placebo, patients switching from ustekinumab were less likely to achieve complete psoriasis clearance. This may be because their psoriasis is more resistant to treatment.

Table 4: Clinical responses at week 52 after switching to brodalumab 210mg Q2W (as observed) (from CS, Table 18, page 54)

	AMAGINE-2		AMAGINE-3	
Outcome	**Brodalumab 210 mg Q2Wafter placebo N = 297**	**Brodalumab 210 mg Q2W after ustekinumab N = 55**	**Brodalumab 210 mg Q2Wafter placebo N = 298**	**Brodalumab 210 mg Q2W after ustekinumab N = 69**
PASI 75, n/N′ (%)	233/248 (94)	40/44 (91)	240/257 (93)	49/60 (82)
95% CI of %	(90–97)	(78–98)	(90–96)	(70–91)
PASI 100, n/N′ (%)	153/248 (62)	20/44 (46)	174/257 (68)	24/60 (40)
95% CI of %	(55–68)	(30–61)	(62–73)	(28–54)
sPGA 0/1, n/N′ (%)	215/248 (87)	32/44 (73)	231/257 (90)	42/60 (70)
95% CI of %	(82–91)	(57–85)	(86–93)	(57–81)
sPGA 0, n/N′ (%)	153/248 (62)	20/44 (46)	174/257 (68)	24/60 (40)
95% CI of %	(55–68)	(30–61)	(62–73)	(28–54)
PSI response, n/N′ (%)[a]	174/216 (81)	31/37 (84)	188/219 (86)	37/51 (73)
95% CI of %	(75–86)	(68–94)	(81–90)	(58–84)

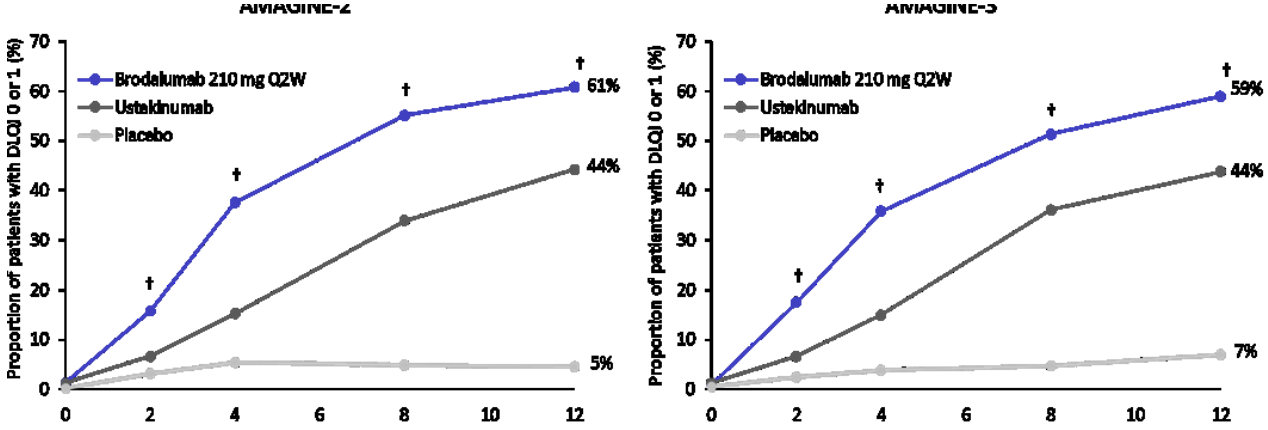
N = number of patients who entered maintenance phase (or qualified for rescue); N′ = number of patients who had a valid measurement value at the specified week; % = n/N′ x 100;
The brodalumab after placebo group started receiving brodalumab at week 12; the brodalumab after ustekinumab group started receiving brodalumab at week 16.
As observed analysis with no imputation – values may not be directly comparable with other tables (see section B.2.4.4).
[a] PSI response was defined as a total score of ≤ 8 with no item > 1
CI, confidence interval; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: Lebwohl *et al.* 2015[31]

Health-related quality of life

Figure 5 shows the proportion of patients with a DLQI score of 0 or 1 (indicating no effect on a patient's life) during the induction phase. Proportions were statistically significantly higher in the brodalumab group than placebo at all time points measured after baseline (p=0.001). Proportions were also higher with brodalumab than with ustekinumab (e.g. at week 12 in

AMAGINE-2: 60.8% vs 44.3%, AMAGINE-3: 59% vs 43.8%) but statistical significance is not reported.[29, 30, 35]

Figure 5: Proportion of patients with DLQI score of 0 or 1 during induction phase (FAS, NRI) (from CS, Figure 15, page 55)



Missing values were imputed as nonresponses (see section B.2.4.4 of CS).
† $p < 0.001$ vs placebo.
DLQI, Dermatology Life Quality Index; FAS, full analysis set; NRI, non-responder imputation.
Source: AMAGINE-2 CSR[29]; AMAGINE-3 CSR[30].

In AMAGINE-2 the proportion of patients that had a clinically significant (≥5-point) improvement in DLQI score at week 12 was 88.4% (95% CI 85.4-90.9) in the brodalumab group, compared with 83% in the ustekinumab group and 29% in the placebo group; the difference between brodalumab and placebo was statistically significant (p<0.001). In AMAGINE-3 the proportion of patients that had a clinically significant improvement in DLQI score at week 12 was 86.7% (95% CI 83.6-89.4) in the brodalumab group, compared with 85% in the ustekinumab group and 31% in the placebo group; the difference between brodalumab and placebo was statistically significant (p<0.001).[29, 30]

Of those patients receiving brodalumab at week 52, [redacted] in AMAGINE-2 and [redacted] in AMAGINE-3 had DLQI scores of 0 or 1, compared with [redacted] and [redacted] of patients receiving ustekinumab.[29, 30] Although the proportion is [redacted] for brodalumab patients, no statistical analysis was performed.

Health-related quality of life in patients switching to brodalumab

Among patients switching from placebo to brodalumab [redacted] had DLQI scores of 0 or 1 at week 52. Among patients switching from ustekinumab to brodalumab rescue therapy [redacted] had DLQI scores of 0 or 1 at week 52. Again, this may suggest that patients who switched from ustekinumab to brodalumab rescue therapy had psoriasis that is more resistant to treatment than those switching from placebo to brodalumab.[29, 30]

Overall, there was a statistically significantly greater impact on quality of life in those treated with brodalumab compared with placebo. However, while results suggest it was more effective than ustekinumab on some of the quality of life measures, statistical significance was not reported.

AMAGINE-1

Psoriasis severity

Table 5 shows key outcomes for the AMAGINE-I trial. The PASI 75 response rate at week 12 was 83.3% for the brodalumab group compared with 2.7% for placebo (p <0.001).[32] PASI 75, PASI 100, PASI 90, sPGA response, sPGA 0 and PSI response were significantly higher in the brodalumab group than the placebo group at week 12.[32] [redacted] [33]

Table 5: Summary of clinical outcomes in AMAGINE-1 (FAS, NRI) (from CS, Table 19, page 58)

	Week 12		Week 52 [a]	
Endpoint	**Placebo (N = 220)**	**Brodalumab 210 mg Q2W (N = 222)**	**Placebo (N = 84)**	**Brodalumab 210 mg Q2W (N = 83)**
PASI 100 response, n (%)	1 (0.5)	93 (42) [†]	0 (0)	56 (67) [†]
PASI 90 response, n (%)	2 (0.9)	156 (70) [†]	0 (0)	65 (78) [†]
PASI 75 response, n (%)	6 (3)	185 (83) [†]	0 (0)	72 (87) [redacted]
sPGA 0 (clear), n (%)	1 (0.5)	93 (42) [†]	0 (0)	56 (67) [†]
sPGA response (0 or 1), n (%)	3 (1)	168 (76) [†]	0 (0)	69 (83) [†]
PSI response, n (%) [b]	9 (4)	135 (61) [†]	[redacted]	[redacted]

[a] Patients who received brodalumab 210 mg until week 12, had an sPGA response (0 or 1) at week 12 and were re-randomised to placebo or brodalumab 210 mg.
[b] PSI response was defined as total PSI score ≤ 8, with no individual item score > 1.
[†] Adjusted *p* value (vs placebo) < 0.001
FAS, full analysis set; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: Papp *et al.* 2016[32]; brodalumab SmPC[36]; AMAGINE-1 CSR[33].

All response outcomes in Table 5 were higher in patients treated with brodalumab at week 52 than they were at week 12. However the patients receiving brodalumab 210mg Q2W at week 52 were only those treated with this dose in the induction phase, who had an sPGA response and were re-randomised to the same treatment for the maintenance phase. Among just these patients (n=83), the proportion achieving PASI 100 increased by week 52 ([redacted] at week 12, 67% at week 52). sPGA, PASI 90 and PASI 75 response rates in this group all [redacted] by week 52 but remained over 75% and [redacted].

Withdrawal and re-treatment

Of 84 patients who achieved an sPGA response with brodalumab in the induction phase and were re-randomised to placebo, 79 patients experienced a return of their psoriasis (sPGA ≥3). After 12 weeks of re-treatment with brodalumab, 97% achieved an sPGA response again, with 84% achieving an sPGA score of 0.[32] The median time to recapture sPGA response was 4.1 weeks.

Health-related quality of life

A statistically significantly higher proportion of patients treated with brodalumab compared with placebo had a clinically meaningful change in DLQI score (≥5-point improvement) at week 12 (83.6% vs 21.6% p <0.001). 55.9% of brodalumab patients had DLQI scores of 0 or 1, compared with 5.0% in the placebo group.[33, 35]

Mean EQ-5D scores were significantly higher in the brodalumab group than placebo at [redacted], week 8 and week 12 (p<0.001). At week 12, the least squares mean difference between groups was [redacted].[33, 37]

There were also statistically significant reductions in mean HADS depression and anxiety scores with brodalumab compared with placebo. The least squares mean treatment difference was -2.1 for depression and -1.5 for anxiety (p < 0.001).[32] Among those patients that had moderate to severe depression or anxiety at baseline, improvements were numerically more likely with brodalumab than placebo.[32]

Open label extension

Table 6 shows PASI and sPGA responses for patients in the long-term extension phase of the three trials. This includes patients treated with ustekinumab throughout the maintenance phase who were switched to brodalumab 210mg Q2W at week 52.[34, 38] This phase was open label and uncontrolled. No imputation was used in the analysis of this data despite a number of patients lost to follow up so the CS highlights that observations should be treated with caution. It is therefore difficult to interpret these data in any detail but they suggest responses were maintained in many patients.

Table 6: Summary of PASI and sPGA responses during open-label long-term extension phase (as observed) (from CS, Table 24, page 65)

	Week	Brodalumab 210 mg Q2W		
		AMAGINE-1 (N = 470)	AMAGINE-2 (N = 1392)	AMAGINE-3 (N = 1403)
PASI endpoints				
PASI 75	52 108 120	[redacted]	[redacted]	[redacted]
PASI 90	52 108 120	[redacted]	[redacted]	[redacted]
PASI 100	52 108 120	[redacted]	[redacted]	[redacted]
sPGA endpoints				
sPGA response (0 or 1)	52 108 120	[redacted]	[redacted]	[redacted]
sPGA 0	52 108 120	[redacted]	[redacted]	[redacted]

All data are n/N (%). Data are as observed, with no imputation.
52-week data include patients treated with other doses of brodalumab, or with ustekinumab up to week 52 before changing to brodalumab 210 mg Q2W in the open-label extension phase.
PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: Long-term extension phase CSRs: AMAGINE-1[39], AMAGINE-2[38] and AMAGINE-3[34].

In response to a request for clarification, the company provided Table 7 which includes results for only those patients who were treated with brodalumab 210mg Q2W throughout the maintenance phase (weeks 12-52) as well as the long-term extension phase. Again, these data are based on an as observed analysis but suggest maintenance of response in many patients.

Table 7: Summary of PASI and sPGA responses during open-label long-term extension phase (as observed): Only brodalumab 210mg Q2W as maintenance therapy (from company's points for clarification response, Table 24B)

	Week	Brodalumab 210 mg Q2W		
		AMAGINE-1 (N = 371)	AMAGINE-2 (N = 581)	AMAGINE-3 (N = 584)
PASI endpoints				
PASI 75	52	[redacted]	[redacted]	[redacted]
	108			
	120			
PASI 90	52	[redacted]	[redacted]	[redacted]
	108			
	120			
PASI 100	52	[redacted]	[redacted]	[redacted]
	108			
	120			
sPGA endpoints				
sPGA response (0 or 1)	52	[redacted]	[redacted]	[redacted]
	108			
	120			
sPGA 0	52	[redacted]	[redacted]	[redacted]
	108			
	120			

All data are n/N (%). Data are as observed, with no imputation.
These analyses include patients only at brodalumab 210 mg Q2W both during maintenance and the open-label extension phase.
PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; sPGA, static physician global assessment.
Source: New analyses based on long-term extension phase CSRs: AMAGINE-1[39], AMAGINE-2[38] and AMAGINE-3[34].

Phase II trials

The SLR identified two phase II RCTs that were included in the NMA but were not described in the CS. In one of these RCTs (Papp et al, 2012[27]), 198 patients were randomised to placebo or one of four doses of brodalumab. There were 38 patients randomised to placebo and 40 patients randomised to brodalumab 210mg Q2W. The primary endpoint differed from the AMAGINE trials as it was the percentage improvement in PASI score. Mean improvements at week 12 were 86.3% in the brodalumab 210mg Q2W group and 16.0% in the placebo group ($p < 0.001$). For PASI 75, PASI 90, PASI 100 and sPGA 0 or 1, brodalumab 210mg Q2W was statistically significantly more effective than placebo at week 12. PASI 75, PASI 90 and sPGA response rates were similar to those in the AMAGINE trials. PASI 100 response rates in those receiving brodalumab 210mg Q2W were much higher (62% at week 12) than in any of the three AMAGINE trials (37-44%) but results are based on much smaller numbers of patients.

In the other RCT (Nakagawa et al. 2016[26]) 38 Japanese patients (of a total 151) were randomised to placebo and 37 to brodalumab 210mg Q2W. Mean improvements in PASI

score were 96.8% with brodalumab 210mg Q2W and 9.4% with placebo at week 12 (p <0.001). PASI 75, PASI 90, PASI 100 and sPGA (0 or 1) response rates were all statistically significantly higher with brodalumab 210mg Q2W than placebo. Response rates for the brodalumab 210mg Q2W arm were all higher than the response rates seen in the AMAGINE trials (e.g. PASI 75: 94.6% vs 83-86% in AMAGINE trials) , although again this is based on much smaller numbers of patients.

Subgroup analyses

Analyses were performed on the following subgroups:

- severity of psoriasis (PASI < 20 or ≥ 20)
- severity of psoriasis (DLQI ≤ 10, > 10 or missing)
- previous use of systemic non-biological therapy or phototherapy (yes or no)
- previous use of systemic non-biological therapy (yes or no)
- number of previous systemic non-biological therapies (0, 1 or ≥ 2)
- non-biological systemic agent failure or contraindication (yes or no)
- previous use of psoriasis biological therapy (yes or no)
- previous failure of psoriasis biological therapy (yes or no)
- previous use of anti-TNF therapy (yes or no)

Subgroup analyses were performed for each AMAGINE-trial separately and for a pooled patient population from all three trials. Subgroup analyses were on PASI 75, 90 and 100 response rates at week 12. [redacted].

However, as shown in the subgroup analysis results of brodalumab versus placebo (Table 91, Appendix E of the CS), [redacted].

The ERG requested further information on a subgroup analysis based on baseline patient weight (≤100 kg versus >100 kg), referred to in the European Medicines Agency (EMA) report on brodalumab.[40] The company clarified that significant differences were seen in the

subgroup analysis according to baseline weight, but as weight based dosing is outside the licence for brodalumab the results were not provided in detail in the CS. Further details were provided by the company. In AMAGINE-2 sPGA, PASI 75 and PASI 100 response rates were lower at week 12 in the subgroup of brodalumab patients with baseline body weight > 100 kg compared with patients with a body weight ≤ 100 kg; sPGA response 66.8% versus 83.6%, PASI 75 response 76.6% versus 90.4%, PASI 100 response 33.7% versus 49.1%. Subgroup analysis results were also provided for PASI 75 response in AMAGINE-3; 76.5% brodalumab patients with baseline body weight > 100 kg achieved PASI 75 response at week 12, compared with 88.2% brodalumab patients with baseline body weight ≤ 100 kg.

Withdrawals

In both AMAGINE-2 and AMAGINE-3, the proportion of randomised patients across all treatment arms that completed the 12-week induction phase was 97%. The 52-week maintenance phase was completed by 87% of patients in AMAGINE-2 and 88% of patients in AMAGINE-3. In AMAGINE-1, 96% completed the 12-week induction phase.[31] Data on withdrawals in the later stages of AMAGINE-1 (presented in Figure 36 in the appendix of the CS) are complicated by patients changing treatments in the maintenance/withdrawal phase. However the ERG notes that the proportion completing the study through week 52 was lower in those that had not responded to brodalumab 210mg Q2W by week 12 compared to those receiving constant brodalumab 210mg Q2W that had responded by week 12 (69% vs 89%).

The CS states that, for all randomised patients in the three trials, the main reason for patients discontinuing was withdrawal of consent, followed by adverse events and loss to follow-up.[31] However the breakdown of reasons for discontinuation in the appendix (Tables 122, Table 123 and Figure 36) shows that 'Other' was the second most common classification in AMAGINE-2 and AMAGINE-3 and the most common in AMAGINE-1. The CS states that lack of response was not given as a reason for withdrawal in any patients treated with brodalumab 210mg Q2W or ustekinumab.[29, 30]

The ERG asked the company to provide more detail on the discontinuations classified as 'Other' or 'Full consent withdrawn', as these made up the majority of cases. [redacted], although the data presented in Tables 122 and 123 and Figure 36 in the appendix of the CS show only 190 withdrawals for this reason across treatment arms through week 52. It is not clear why the additional data provided by the company differs or which stages of the trials they are based on. [redacted]

[redacted]

[redacted]

4.2.3.2 Safety

The safety analysis set (SAS) included all randomised patients who received at least one dose of investigational product. For AMAGINE-2 and AMAGINE-3, the safety analysis presented in the main submission focuses on just patients who received constant brodalumab 210mg Q2W or ustekinumab throughout the trials, although for the maintenance phase this includes those randomised to placebo and re-randomised to brodalumab 210mg Q2W at week 12 (according to Table 33 and 34 of the CS). For AMAGINE-1, it focuses on just those who received brodalumab 210mg Q2W or placebo during the induction phase and constant brodalumab 210mg Q2W throughout the maintenance phase. [redacted] For AMAGINE-1 the CS provides data on mean exposure for all patients who received at least one dose of brodalumab, including unlicensed or mixed dosing (291 days, SD 83.7 days).[33]

Table 8 shows proportions and rates of adverse events across the relevant treatment arms. During the 12 week induction phase of AMAGINE-2 and AMAGINE-3, the proportion of patients with an adverse event was higher in the brodalumab 210mg Q2W and ustekinumab groups than in the placebo group. Rates were similar between the brodalumab and ustekinumab groups (59.0% ustekinumab vs 57.8% brodalumab).[31] The CS states that in AMAGINE-1 the proportion of patients with adverse events in the induction phase was similar in the brodalumab and placebo groups,[32] although the ERG notes that the data in Table 8 shows that it was higher in the brodalumab group (50.9% placebo vs. 59.0% brodalumab).

According to the CS, the frequency of events that lead to discontinuation of treatment or from the study was low and similar across groups throughout the 52 weeks in all three AMAGINE trials.[31] [32] However the ERG notes that the data show these rates to be higher with brodalumab than ustekinumab in the maintenance phase of AMAGINE-2 and AMAGINE-3. The rate of adverse events was similar for ustekinumab and brodalumab in the maintenance phase of the AMAGINE-2 and AMAGINE-3 trials. Table 102 in the appendix of the CS presents data on the overall rate of treatment-emergent adverse events in all patients exposed to brodalumab in the three trials, including the open-label extension phases, which is [redacted]

Table 8 Summary of adverse events in the AMAGINE trials (based on SAS, adapted from CS, Table 33, page 80 and Table 36, page 86, source: Lebwohl et al 2015[31])

Induction phase (to week 12) **Adverse event, n (%)**	**AMAGINE-2**			**AMAGINE-3**			**AMAGINE-1**	
	Placebo n=309	**Ustekinumab n= 300**	**Brodalumab, 210 mg Q2W n = 612**	**Placebo n= 313**	**Ustekinumab n= 313**	**Brodalumab 210 mg Q2W n = 622**	**Placebo n = 220**	**Brodalumab 210 mg Q2W n = 222**
Any	165 (53.4)	177 (59.0)	354 (57.8)	354 (57.8)	168 (53.7)	353 (56.8)	112 (50·9)	131 (59·0)
Serious	8 (2.6)	4 (1.3)	6 (1.0)	6 (1.0)	2 (0.6)	9 (1.4)	3 (1·4)	4 (1·8)
Fatal	0	0	1 (0.2)	1 (0.2)	0	0	0	0
Leading to discontinuation of study	0	2 (0.7)	6 (1.0)	6 (1.0)	1 (0.3)	5 (0.8)	3 (1·4)	2 (0·9)
Leading to discontinuation of drug	1 (0.3)	4 (1.3)	6 (1.0)	6 (1.0)	2 (0.6)	7 (1.1)	3 (1·4)	2 (0·9)
Grade 3, 4, or 5	10 (3.2)	11 (3.7)	25 (4.1)	25 (4.1)	8 (2.6)	23 (3.7)	9 (4·1)	15 (6·8)

	AMAGINE-2		**AMAGINE-3**		**AMAGINE-1**
Maintenance phase (to week 52) **Adverse event, n (exposure-adjusted event rate per 100 patient-years)**	**Constant ustekinumab n = 300**	**Constant brodalumab, 210 mg Q2W)[a] n = 486**	**Constant ustekinumab n= 313**	**Constant brodalumab 210 mg Q2W[a] n = 489**	**Constant brodalumab 210 mg Q2W n = 345**
Exposure, patient-years	246.1	379.7	248.6	383.5	271.8
Any	1,017 (413.3)	1,531 (403.2)	935 (376.1)	1,522 (396.8)	1034 (380·4)
Serious	32 (13.0)	38 (10.0)	10 (4.0)	31 (8.1)	27 (9·9)
Fatal	2 (0.8)	1 (0.3)	0	0	3 (1·1)
Leading to discontinuation of study	3 (1.2)	14 (3.7)	4 (1.6)	12 (3.1)	9 (3·3)
Leading to discontinuation of drug	10 (4.1)	18 (4.7)	7 (2.8)	15 (3.9)	10 (3·7)
Grade 3, 4, or 5	61 (24.8)	57 (15.0)	29 (11.7)	59 (15.4)	55 (20·2)

a Constant brodalumab 210mg Q2W group includes patients randomised to placebo and re-randomised to brodalumab 210mg Q2W at week 12

Common adverse events

The most common adverse events in the induction phase of AMAGINE-2 and AMAGINE-3 were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Nasopharyngitis, headache and arthralgia were more frequent in the brodalumab groups than with placebo or ustekinumab in AMAGINE-2. In AMAGINE-3, arthralgia was more frequent with brodalumab than placebo or ustekinumab.[31] In AMAGINE-1, the most common adverse events in the induction phase were nasopharyngitis, upper respiratory tract infection and headache, with the latter two occurring more frequently in the brodalumab group than placebo.[32]

Adverse events of interest

In AMAGINE-2 and AMAGINE-3, the most common adverse events of interest according to the CS were injection site reactions in the induction phase, occurring at a similar frequency across the groups, and injection site reactions and candida infections during the maintenance phase. Candida infections were more frequent in patients receiving brodalumab 210mg Q2W than in the ustekinumab or placebo groups in both phases.[31] The CS states that this is consistent with the known role of IL-17 in mediating the immune response to fungal infections[41] and it was confirmed by the clinical advisor to the ERG that IL-17 inhibitors cause an increased risk of candida infection. All candida infections were graded as mild or moderate and were not systemic.[31] In AMAGINE-1, the most common adverse event of interest according to the CS was candida infection but all cases were mild to moderate.[32]

Suicidal ideation was experienced by some patients in the AMAGINE-2 and AMAGINE-3 trials.[31] This is discussed in more detail below.

Serious adverse events

In the induction phase, the incidence of serious adverse events across AMAGINE-2 and AMAGINE-3 was 1.8% for placebo, 1.0% for ustekinumab and 1.2% for brodalumab. The most common serious adverse events across the two trials were infections and infestations, which were slightly more common in the brodalumab group.[31] During the maintenance phase, the rate of patients reporting serious adverse events was similar in the brodalumab and ustekinumab groups.[31] In AMAGINE-1, the overall incidence of serious adverse events during the induction phase was 1.8% with brodalumab 210mg Q2W and 1.4% with placebo.[31] During the maintenance phase, the exposure-adjusted event rate of treatment-emergent serious adverse events for patients exposed to brodalumab 210mg Q2W was 9.9 events per 100 patient-years.[32]

Deaths

Across all treatment arms in AMAGINE-2 and AMAGINE-3, one death occurred during the induction phase, five during the maintenance phase, three after patients had stopped receiving treatment with brodalumab and [redacted] Of particular interest to regulators were two deaths from completed suicide in patients that had received brodalumab (one in AMAGINE-2 27 days after the last dose, [redacted]). Four patients died in AMAGINE-1 during the maintenance phase and one of these was an illicit drug overdose originally classified as suicide. There was also a death due to suicide during the open-label extension phase (59 days after the last dose).[32]

Further details of deaths in the AMAGINE trials are provided in the CS and suicide is discussed in more detail below.

Suicide, suicidal ideation and behaviour

Some patients in the AMAGINE trials experienced SIB and overall there were four completed suicides, although one was later adjudicated as indeterminate. All of the three other suicides were after the end of exposure to brodalumab ([redacted] days after the last dose). There were also three suicide attempts in the brodalumab 210mg Q2W group during the induction and maintenance phases of AMAGINE-2, although these were all by the same patient.[31] From March 2014, the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) was added to the three AMAGINE trial protocols.[34, 38, 39] [redacted]

Section B.2.10.5 of the CS provides further information and summarises some of the evidence on the risk of SIB, concluding that the data suggest that the risk of SIB is not higher with brodalumab than with other biological therapies. This is based on an independent analysis of SIB in trials of biological therapies for psoriasis conducted by the FDA.[42] The overall rate of suicidal behaviour (attempted and completed suicide) was found to be 0.14 events per 100 patient-years for brodalumab. The analysis found higher rates of suicidal behaviour with infliximab and apremilast.[42] The same rate is observed in patients treated with ixekizumab, despite patients with a risk of suicidal behaviour being excluded from the ixekizumab trials but not from the AMAGINE trials of brodalumab.[42] However the ERG notes that the cited report highlights the fact there were no completed suicides with ixekizumab as a key difference compared with brodalumab.[42]

The CS also describes a review of published data on psoriasis therapies (performed by Valeant Pharmaceuticals and submitted to the FDA) which found SIB event rates for brodalumab to be consistent with other therapies.[43] The completed suicide rate was 0.04 (95% CI 0.01 to 0.11) per 100 patient-years in the brodalumab psoriasis program compared with a rate of 0.03 (95% CI 0.01 – 0.06) observed in external trials and registry data for other agents.[44] However the ERG notes that the rate of suicide attempts was higher in the brodalumab psoriasis program (0.109 95% CI 0.052-0.201) compared with the external pooled estimate (0.04 95% CI 0.01 to 0.10).[43]

The ERG also notes that the FDA report on brodalumab expresses uncertainty over the risk of suicide with brodalumab and is not able to draw firm conclusions.[45] Likewise, the EPAR report concludes that although current data does not establish causality, SIB are a potential risk with brodalumab. This potential risk is considered balanced with implemented information for the prescriber and the patient in the product information and will be followed up upon by means of a post authorisation safety study.[40] The SPC also includes warnings and precautions on SIB.[36] Overall the ERG considers that the company's conclusion on the risk of SIB may not be supported by the evidence which so far does not appear sufficient to draw firm conclusions on a relationship between brodalumab and SIB.

4.2.4 Supporting data from non-RCTs

Four additional publications were described in the appendix, identified from searches for non-RCT evidence; all were open-label extension studies including less than 200 patients. Results were generally consistent with those of the open label extension phase of the AMAGINE trials, suggesting that PASI responses were maintained in the majority of patients beyond 52 weeks.

4.2.5 Conclusions from critique of trials of the technology of interest

The AMAGINE trials were good quality RCTs and the results are likely to be reliable. Trial inclusion criteria appear to have been appropriate and baseline characteristics were similar across treatment groups. However, inclusion criteria relating to disease severity were not the same as the threshold specified in the NICE treatment pathway. In addition, 17-35% patients had not received previous systemic therapy or phototherapy, which is not consistent with the proposed positioning of brodalumab in the treatment pathway. The trials also excluded patients who had previously received ustekinumab or anti-IL-17 therapy, which may not be reflective of how brodalumab would be positioned in practice. Therefore, the results of the AMAGINE trials may not be entirely generalisable to the proposed eligible population.

Across the three AMAGINE trials withdrawal rates in patients treated with brodalumab were low with around 88% completing the study to week 52; for patients receiving the 210 mg Q2W dose, 81-82% patients completed the study to week 52. The ERG notes this is comparable with the drug survival rates published for other biologics.[21]

All three trials demonstrated that brodalumab 210mg Q2W significantly reduced the severity of psoriasis and its impact on health-related quality of life compared with placebo. A statistically significant difference was found between brodalumab 210mg Q2W and placebo for all the outcomes reported at week 12 [redacted]. The AMAGINE-2 and AMAGINE-3 trials compared brodalumab with ustekinumab and demonstrated that patients taking brodalumab 210mg Q2W were statistically significantly more likely to achieve a PASI 100 response, PASI 90 response, sPGA score of 0 or 1, sPGA score of 0 and PSI response at 12 weeks. The PASI 75 response rate was significantly higher with brodalumab 210mg Q2W than ustekinumab in AMAGINE-3 but statistical significance was not reported for AMAGINE-2. The proportion of patients with a DLQI score of 0 or 1 or ≥ 5-point improvement in DLQI score was numerically higher with brodalumab compared with ustekinumab but statistical significance was not assessed. At 52 weeks in AMAGINE-2 and AMAGINE-3, PASI 75, PASI 90, PASI 100, sPGA responses and the proportion of patients with DLQI scores of 0 or 1 were numerically higher with brodalumab compared with ustekinumab, although statistical significance was not assessed. In those patients who continually received brodalumab 210mg Q2W or ustekinumab throughout the study, PASI 75 and PASI 90 response rates were maintained to week 52, while PASI 100 response rates increased slightly. Data are not provided on relapse rates so it is not possible to know if all patients achieving these thresholds at week 12 maintained their response. The long-term extension phase of the three trials was open label and uncontrolled, with no imputation used in the analysis of missing data. It is therefore difficult to interpret these data in any detail but they suggest responses were maintained in many patients.

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

A NMA is presented which compares the efficacy of brodalumab with the licensed therapies adalimumab, apremilast, etanercept, infliximab, ixekizumab, secukinumab, ustekinumab and DMF. The base-case NMA includes both licensed doses of the therapies specified in the scope, along with unlicensed doses and conventional systemic therapies, where their inclusion was considered to contribute additional indirect evidence for licensed doses. Different dosing schedules of etanercept 25 mg twice weekly and 50 mg once weekly were pooled into a single etanercept 50 mg per week treatment arm in the base case results. For all other drugs

different doses and/or dosing regimens were treated as unique comparators. A sensitivity analysis was undertaken which included only licensed doses and dosing regimens currently recommended by NICE (sensitivity analysis 1), which is consistent with NMAs undertaken in other recent STAs of treatments for moderate to severe plaque psoriasis in adults (apremilast, ixekizumab and DMF).[46-48]

A systematic literature review was conducted to identify all potentially relevant RCTs for inclusion in the NMA. The company submission describes the search strategies used to identify relevant RCTs of brodalumab and potential comparator therapies (secukinumab, etanercept, infliximab, adalimumab, ustekinumab, apremilast, ixekizumab, DMF) used for the treatment of moderate to severe plaque psoriasis. The search strategies are presented in Appendix D.1.1 of the submission (pages 177 to 188). The database searches were carried out on 31st August 2016 and updated on 25th July 2017, with searches for trials of DMF carried out on 8th August 2017. The following databases were searched: MEDLINE, MEDLINE in Process, EMBASE, and the Cochrane Library. A number of conference proceedings were also scanned from 2013 onwards: International Society for Pharmacoeconomics & Outcomes Research (ISPOR); World Congress of Dermatology; and American Academy of Dermatology. The reporting of the searches was clear with sufficient detail to allow the database searches to be reproduced. The ERG notes that the searches of the Cochrane Library included redundant publication type search terms; these are not necessary as the content of this resource is already filtered by publication type.

The inclusion criteria used to select studies for inclusion in the NMA appear to have been appropriate. The first phase of study selection, screening titles and abstracts of the studies identified from electronic databases, was performed in duplicate, minimising the risk of reviewer error and bias. However, it is unclear whether the second phase, screening full texts of studies, was undertaken in a similar manner. A PRISMA flow diagram is presented as Figure 33 of the CS, along with a table of excluded studies with reasons for exclusion (Table 80 of the CS). The PRISMA flow diagram presented in the CS contained a few errors; a corrected PRISMA diagram was provided in response to the ERG's request for clarification. Data were extracted on the proportion of patients who achieved PASI 50, PASI 75, PASI 90 and PASI 100 at the end of the study-defined induction period. Studies were assessed for quality using appropriate criteria; the results of the quality assessment (presented in Table 87, Appendix D of the CS) suggest that overall, the risk of bias for most studies was low.

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 earlier STAs of secukinumab, apremilast, ixekizumab and DMF was undertaken. No relevant trials appear to have been excluded from the NMA.

The network diagram of evidence included in the base case NMA is presented as Figure 25 in the submission. The base case NMA included data from 59 RCTs involving 28,346 patients. All included studies were conducted in patients with moderate to severe plaque psoriasis who were eligible for systemic therapy. All studies reported data at the end of a short-term induction period, the length of which varied by treatment (infliximab, 10 weeks; brodalumab, etanercept, ixekizumab, secukinumab and ustekinumab, 12 weeks; adalimumab, apremilast and DMF, 16 weeks).

The CS presents adequate details of the studies included in the NMA. Baseline patient characteristics are presented in Table 83 of the submission. In general, patient characteristics were broadly similar across trials. When comparing the AMAGINE trials with other trials in the network, DLQI score was generally slightly higher (worse quality of life) in patients in the AMAGINE trials than in most of the other trials, where reported. Also, the proportion of patients who had received prior biological therapy was also slightly higher in the AMAGINE trials than many of the other studies included in the network. The CS states that higher levels of previous biologic therapy were seen in more recent trials, whilst in some trials it was a requirement that patients were biologic-naïve. The CS discusses differences in patient populations of trials included in the NMA (page 204 of the CS). The mean weight of participants in Asian studies was typically lower and the mean disease duration was somewhat shorter in four of the trials than in other studies. One trial had a considerably higher proportion of patients who also had psoriatic arthritis. There was considerable variation in the proportion of patients who had received previous phototherapy across the studies, and in the proportion who had received previous conventional systemic therapies. Sensitivity analyses were conducted to address differences in population characteristics across the trials (sensitivity analysis 4 excluded studies in which more than 30% randomised patients reported having previously tried biological therapy and sensitivity analysis 5 excluded studies with a mean baseline PASI score of greater than 25).

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

4.4.1 Critique of the NMA methods

The NMA results presented were PASI response rates (PASI 50, PASI 75, PASI 90 and PASI 100), which is an appropriate outcome for patients with moderate to severe psoriasis and consistent with previous NICE STA submissions for psoriasis therapies. The CS stated that other outcomes were either poorly or inconsistently reported across studies and were therefore

not prioritised for synthesis. However, NMAs undertaken for the development of the British Association of Dermatologists' (BAD) guidelines for biologic therapy for psoriasis, published in April 2017, also assessed mean change in DLQI score and tolerability in their NMA.[49]

A Bayesian NMA model was undertaken using a probit model for ordered multinomial outcomes of PASI response rates. Fixed- and random-effects approaches were explored. The random-effect 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 pooled absolute and relative effects for evaluated interventions at each level of PASI response are reported in Tables 26 to 28 of the company submission. The synthesis model followed the general principles outlined in the NICE DSU technical support document.[50]

Adjustment for differences in placebo response rates across the trials

An important difference identified between the trials included in the NMA was the observed PASI response rates in the placebo arms of the trials, which is the common reference treatment across the majority (n=49, 83%) of the trials. Table 84 in the submission showed that the PASI 50 response rate in the placebo arm of the trials included in the NMA ranged from 5.1% to 33.3%. Similar variability was also reported in the PASI 75 response rate data in the placebo arms which ranged from zero to 20% across all trials (and between 2.7% and 8.1% across the AMAGINE trials). Inevitably the trials included in the NMA vary by design, eligibility criteria, prior medication (including prior use of systemic non-biologic and biologic therapies), average age and other relevant characteristics that might influence the outcome of interest. All of these variations could contribute to differences in placebo response rates and, therefore, to differences in the relative efficacy of the intervention to placebo.

As a means to assess this existing between-study heterogeneity, NMA meta-regression models on baseline risk (i.e. placebo response) were also explored in the company submission.[51, 52] These meta-regression models impose a common interaction effect between baseline risk and relative effectiveness that account for variation in reference arm response across trials. The common interaction assumption is the least data demanding (i.e. only one extra parameter is needed to be estimated), but it also imposes the strongest assumption as it implies that the same placebo effect exists across evaluated interventions (excluding placebo).[53]

Signorovitch et al. notes that "*To assess the extent of confounding and bias that could arise from lack of adjustment for reference arm response*" … "*the 95% credible interval (CrI)*" of the estimated β coefficient should be obtained, where "*an interval not containing 0 would indicate significant statistical evidence against the 'unadjusted' model*" and that "*the*

variance of the random effect, which provides a measure of between trial heterogeneity, and the deviance information criterion (DIC), which provides a measure of model fit that penalizes model complexity," should be *"compared between the adjusted and unadjusted models"*.[52] The ERG would also add that the total residual deviance is also a useful statistic to compare models.[50]

A comparison of unadjusted and adjusted models was reported in Table 32 of the submission. The estimated reference arm adjustment coefficient, β, was estimated to be -0.68 (median, 95% CrI -0.86 to -0.50) and is statistically significantly different from zero. This indicates that, compared to the unadjusted model, the placebo adjustment reduced unexplained heterogeneity and improved the model. In addition, the 95% CrI of the random effect, τ, was estimated to be from 58.49 to 336.2 in the adjusted model compared with 44.25 to 423 in the unadjusted model, i.e. the former interval is narrower. This shrinking of the 95% CrI in the adjusted model relative to the unadjusted one demonstrates a reduction in the between-study heterogeneity, which is being captured by the adjustment coefficient, β. The total residual deviance statistic was similar between the two models (unadjusted model: mean of 1,066; adjusted model: mean of 1,067). However, and perhaps contrary to intuition, the DIC for the adjusted model was marginally higher than the DIC for the unadjusted model. As a reminder, a lower DIC implies a better model fit.

In the company submission, the choice concerning the adjusted or the unadjusted synthesis model results to inform the economic model was done based on the DIC, i.e. the unadjusted model was chosen. However, the use of DIC alone ignores other statistical advantages of the placebo adjusted model in terms of goodness of fit and the observed heterogeneity of PASI response rates across included trials. The ERG considers the placebo adjusted synthesis model to be more appropriate than the unadjusted model despite the marginally higher DIC value.

The ERG also requested additional detail on the placebo adjusted model implemented in the submission (clarification point A21a to A21e). Further results were provided (Tables 8 to 11 of the clarification document) together with the WinBUGS code for the placebo adjusted model. The WinBUGS code was assessed by the ERG and minor revisions made. These revisions included centring the baseline effect with the mean value of the observed baseline response of placebo trials on the probit scale and the use of true uninformative priors for relevant parameters. Further details on the revised synthesis model implemented by the ERG and the associated assumptions, including WinBUGS code can be found in Appendix 10.1.

Predicted PASI responses from the revised placebo adjusted synthesis model performed by the ERG are shown in Table 10 (in Section 4.4.2, below). These results are complemented by model estimates of measures of goodness of fit (DIC and total residual deviance) and by the

random effects and placebo adjustment coefficient estimates. The results obtained are very similar to those reported in Table 8 of the company clarification response, with virtually identical predicted absolute PASI responses and equivalent treatment ranking.

The ERG revisions and revised analyses provide important reassurance regarding the company analyses and demonstrate that the revisions made by the ERG, while conferring some potential theoretical advantages, made no material difference to the final results. However, the ERG considers that their revised coding and output provided a more appropriate basis for the further exploratory cost-effectiveness analyses undertaken by the ERG and reported in later sections.

Predicting absolute effects for all treatment contrasts

Both the unadjusted and placebo adjusted synthesis models presented in the submission considered a baseline risk of PASI response estimated separately from the synthesis model (with mean = 1.049 and precision = 367.003). The ERG requested additional detail on how these quantities were estimated (clarification point A22). Further explanation was provided in the company response document, highlighting that, as described in DSU TSD2,[50] PASI 50 response outcomes for placebo from included studies were used to inform the baseline event rates and estimated through separate Bayesian analysis in WinBUGS.

The ERG agrees with the approach used in the submission. However, the ERG also notes that in recognising the existing baseline risk heterogeneity of PASI response across included trials, the heterogeneity in baseline risk across the three pivotal phase 3 RCTs for brodalumab (i.e. the AMAGINE trials) should be considered more explicitly. Thus, a series of additional analyses were undertaken using alternative PASI 50 response outcomes for placebo. This included:

a. Baseline risk of PASI response estimated separately from the three AMAGINE trials only;
b. Baseline risk of PASI response estimated separately from the AMAGINE 1 trial only;
c. Baseline risk of PASI response estimated separately from the AMAGINE 2 and AMAGINE 3 trials only.

Synthesis model variants b. and c. are relevant as these acknowledge the existing differences in baseline characteristics from the AMAGINE 1 and AMAGINE 2 and 3 trials; a higher proportion of patients in AMAGINE-1 had received previous biological therapies than those in AMAGINE-2 and 3. These may be reflected in the difference in PASI 50 placebo response rate of almost 10% between AMAGINE 1 and AMAGINE 2 and 3 (PASI 50 placebo responses: AMAGINE 1: 7.7%; AMAGINE 2: 15.2%; and AMAGINE 3: 18.1%).

Following the methods described in NICE DSU TSD2[50] and applied in the company submission, a separate Bayesian analysis in WinBUGS for each variant was implemented. Further details on the implemented synthesis model variants by the ERG, including WinBUGS code can be found in Appendix 10.1. The following set of mean and precision estimates were obtained for each analysis: a. mean = 1.118 and precision = 32.420; b. mean = 1.460 and precision = 253.700; and c. mean = 0.964 and precision = 98370.000.

4.4.2 NMA results

Predicted PASI responses for evaluated interventions (base case) are presented in Table 26 of the CS. Results for sensitivity analysis 1 are presented in Table 29. In response to the ERG's points for clarification the company provided results for additional sensitivity analyses. Table 9 presents the median probability of achieving a PASI 75 response, comparing the base case analysis results with sensitivity analysis 1 (excluding unlicensed doses/regimens not recommended by NICE), sensitivity analysis 4 (excluding studies in which more than 30% patients reported having previously tried biological therapy) and a sensitivity analysis excluding all phase II trials. When ranked in order of effectiveness, the results for the base case NMA and sensitivity analyses were consistent: ixekizumab, brodalumab, secukinumab, infliximab, ustekinumab, adalimumab, etanercept, apremilast, DMF, placebo.

Table 9: Comparison of PASI 75 results between baseline NMA and sensitivity analyses

Treatment	Probability of PASI 75 response, median (95% CrI)			
	Base case	**Sensitivity analysis 1**	**Sensitivity analysis 4**	**Excluding phase II trials**
Placebo	5.7% (4.6-7.1)	5.5% (4.3-6.9)	6.3% (4.9-7.9)	5.4% (4.3-6.8)
Brodalumab 210mg	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40mg Q2W	66% (59.3-72.1)	63.4% (56.3-70.1)	67.3% (60.1-73.8)	64.5% (57.1-71.2)
Apremilast 30mg BID	27.3% (21.5-33.7)	26.8% (20.7-33.5)	29.2% (22.4-36.8)	26.6% (19.9-34.2)
Etanercept 50 mg / week	39.1% (32.5-46.2)	41.2% (33.4-49.5)	40.5% (33.3-48.1)	37.3% (30.3-44.9)
Infliximab 5mg/kg	79.2% (72.8-84.7)	82.6% (75.5-88.3)	80.6% (73.8-86.6)	78.9% (71.6-85.1)
Ixekizumab 80mg Q2W	90.4% (87-93)	89.4% (85.2-92.7)	90.9% (86.9-93.8)	89.7% (86-92.7)
Secukinumab 300mg	83.6% (79-87.7)	83.4% (78.2-87.9)	84% (78.9-88.3)	82.8% (77.6-87.2)
Ustekinumab 45mg	71.6% (65.5-77.1)	72.9% (66-78.9)	69.9% (61.6-77.4)	70.4% (63.7-76.4)
Ustekinumab 90mg	75.3% (69.3-80.7)	76.9% (70-82.7)	74.8% (65.6-82.6)	74.3% (67.6-80.2)
Ustekinumab (in-label dose)	71% (64.7-76.8)	70.2% (63.5-76.4)	71% (64.1-77.4)	69.4% (62.5-75.8)
DMF	19.3% (11.4-29.9)	18.7% (10.9-29.3)	20.4% (12-31.8)	18.7% (10.7-29.5)

BID, twice daily; CrI, credible interval; DMF, dimethyl fumarate; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

The ERG checked the NMA results against those of a NMA undertaken by the guideline development group for the BAD guidelines for biologic therapy for psoriasis, published in April 2017.[49] The BAD NMA compared ixekizumab, secukinumab, infliximab, ustekinumab, adalimumab, etanercept, methotrexate and placebo. Interventions were ranked in order or efficacy. In terms of short term (3-4 months) clinical benefits, ixekizumab, secukinumab and infliximab consistently ranked best, above ustekinumab, adalimumab, etanercept, methotrexate and placebo, which is consistent with the brodalumab NMA results, for those therapies included in both analyses. For the outcome clear/nearly clear (PASI 90 and/or PGA of 1 or less) at 3-4 months ixekizumab ranked best, followed by secukinumab, infliximab, ustekinumab, adalimumab, etanercept, methotrexate and placebo. For the outcome PASI 75 at 3-4 months ixekizumab ranked best, followed by infliximab, secukinumab, ustekinumab, adalimumab, etanercept, methotrexate and placebo. The NMA undertaken for the BAD guidelines also included an assessment of DLQI and tolerability, which were not included in the brodalumab NMA. For the outcome mean change in DLQI at 3-4 months secukinumab ranked best, followed by infliximab, ixekizumab, ustekinumab, adalimumab, etanercept, methotrexate and placebo. However, in terms of tolerability (withdrawal due to adverse

events at 3-4 months) ustekinumab ranked best, followed by adalimumab, secukinumab, methotrexate, placebo, etanercept, ixikizumab and infliximab.

The pooled relative effectiveness for evaluated interventions at each level of PASI response versus placebo is reported in Table 27 of the CS. The pooled relative effectiveness at each level of PASI response for brodalumab versus the comparators is presented in Table 28 of the CS. In response to the ERG's request for pairwise comparisons of the relative risk (with 95% credible intervals) of achieving PASI 75 response for all interventions in the base case NMA and sensitivity analysis 1 and 4, results are presented in Tables 3, 5 and 7 of the company response.

Results of revised placebo adjusted synthesis model variants

Table 10 and Table 11 summarise the results of the ERG revised placebo adjusted NMA model in terms of absolute PASI response rates, with the baseline placebo PASI response derived from all the trials in the NMA and the three variants using the AMAGINE trials only. The results for the different variants are generally similar to the revised placebo adjusted model using a baseline placebo response derived from all trials. It shows that all active treatments are more effective than placebo and that the treatment rankings reported by the company were unaltered. The main differences, relative to the base-case revised placebo adjusted model, are observed in the variant b. model with a placebo effect for PASI 50 of 7.2% (approximately half of 14.7%, the placebo PASI 50 mean response (Table 11)). This impacted the PASI 50 response rate of the different treatments, for instance, it was reduced for ixekizumab 80 mg Q2W from 96.1% to 94.8%, for brodalumab 210mg from 95.8% to 94.5% and for secukinumab 300mg from 92.5% to 90.4%. The implications of these differences for cost-effectiveness are further explored by the ERG in later sections.

Table 10: Predicted PASI responses for evaluated interventions from the revised random effects placebo adjusted NMA model – ERG revisions

Treatment	Probability of PASI response												Ranking
	PASI 50			PASI 75			PASI 90			PASI100			
	median	95% CrI		median	95% CrI		median	95% CrI		median	95% CrI		
Placebo	14.7%	12.5%	17.2%	5.7%	4.6%	7.0%	1.3%	1.0%	1.6%	0.1%	0.1%	0.2%	13
Brodalumab (210 mg)	[redacted]												2
Adalimumab (40 mg)	85.0%	82.3%	87.3%	69.5%	65.6%	73.0%	43.9%	39.7%	48.0%	17.2%	14.6%	20.0%	8
Apremilast (30 mg)	51.9%	46.8%	56.9%	31.5%	27.1%	36.2%	12.6%	10.2%	15.5%	2.6%	1.9%	3.5%	11
Etanercept (50 mg/week)	59.8%	55.1%	64.5%	39.0%	34.4%	43.8%	17.3%	14.4%	20.6%	4.1%	3.1%	5.4%	10
Etanercept (100 mg/week)	71.2%	68.5%	73.9%	51.2%	48.2%	54.5%	26.4%	23.9%	29.1%	7.7%	6.6%	9.0%	9
Infliximab (5 mg/kg)	90.9%	88.5%	92.9%	78.9%	75.0%	82.5%	55.6%	50.5%	60.8%	25.7%	21.7%	30.2%	4
Ixekizumab (80 mg Q2W)	96.1%	94.9%	97.0%	89.1%	86.6%	91.2%	71.5%	67.2%	75.5%	41.1%	36.4%	45.9%	1
Secukinumab (300 mg)	92.5%	90.6%	94.1%	81.8%	78.5%	84.9%	59.7%	55.0%	64.4%	29.2%	25.2%	33.6%	3
Ustekinumab (45 mg)	85.2%	82.4%	87.7%	69.7%	65.6%	73.7%	44.2%	39.7%	48.8%	17.4%	14.5%	20.6%	7
Ustekinumab (90 mg)	87.0%	84.0%	89.6%	72.5%	68.0%	76.8%	47.4%	42.2%	52.7%	19.5%	16.1%	23.4%	5
Ustekinumab (in-label dose)	85.8%	82.8%	88.5%	70.6%	66.2%	75.0%	45.2%	40.3%	50.4%	18.1%	14.9%	21.7%	6
Dimethyl Fumarate	50.4%	40.1%	60.5%	30.2%	21.8%	39.7%	11.9%	7.5%	17.7%	2.4%	1.3%	4.3%	12
DIC	3097.22												
Total residual deviance *	1067 (1036, 1103)												
Tau, random effect	122.9 (58.59, 348.6)												
β, placebo adjustment coefficient	-0.6854 (-0.851, -0.4981)												

* compared with 573 data points

Table 11: Predicted PASI responses for evaluated interventions from the revised random effects placebo adjusted model variants – ERG revisions

Treatment	Probability of PASI response												Ranking
	PASI 50			PASI 75			PASI 90			PASI100			
	median	95% CrI		median	95% CrI		median	95% CrI		median	95% CrI		
Synthesis model variant a. (baseline risk estimated from the three AMAGINE trials only)													
Placebo	13.2%	7.1%	21.9%	5.0%	2.3%	9.6%	1.0%	0.4%	2.5%	0.1%	0.0%	0.3%	13
Brodalumab (210 mg)	[redacted]												2
Adalimumab (40 mg)	84.6%	80.3%	87.7%	68.8%	62.7%	73.7%	43.1%	36.7%	48.8%	16.7%	12.9%	20.6%	8
Apremilast (30 mg)	51.1%	44.0%	57.5%	30.8%	24.8%	36.7%	12.2%	9.0%	15.8%	2.5%	1.6%	3.6%	11
Etanercept (50 mg/week)	59.0%	52.4%	65.1%	38.2%	32.0%	44.5%	16.8%	12.9%	21.1%	3.9%	2.7%	5.5%	10
Etanercept (100 mg/week)	70.5%	65.6%	75.0%	50.4%	45.0%	55.8%	25.7%	21.5%	30.2%	7.4%	5.7%	9.5%	9
Infliximab (5 mg/kg)	90.5%	87.3%	93.1%	78.3%	73.0%	83.0%	54.7%	48.0%	61.4%	25.0%	19.9%	30.8%	4
Ixekizumab (80 mg Q2W)	95.9%	94.2%	97.1%	88.6%	85.2%	91.5%	70.7%	64.9%	76.1%	40.2%	34.1%	46.7%	1
Secukinumab (300 mg)	92.1%	89.5%	94.3%	81.2%	76.6%	85.3%	58.8%	52.5%	65.1%	28.4%	23.3%	34.3%	3
Ustekinumab (45 mg)	84.7%	80.6%	88.2%	69.0%	63.2%	74.4%	43.3%	37.2%	49.7%	16.8%	13.1%	21.2%	7
Ustekinumab (90 mg)	86.5%	82.5%	89.9%	71.7%	65.8%	77.3%	46.5%	39.9%	53.4%	18.9%	14.7%	24.0%	5
Ustekinumab (in-label dose)	85.3%	81.0%	88.8%	69.9%	63.7%	75.5%	44.4%	37.7%	51.0%	17.5%	13.5%	22.2%	6
Dimethyl Fumarate	49.6%	38.0%	60.4%	29.5%	20.2%	39.6%	11.5%	6.7%	17.7%	2.3%	1.1%	4.3%	12
Synthesis model variant b. (baseline risk estimated from the AMAGINE 1 trial only)													
Placebo	7.2%	5.7%	9.1%	2.3%	1.7%	3.1%	0.4%	0.3%	0.6%	0.0%	0.0%	0.0%	13
Brodalumab (210 mg)	[redacted]												2
Adalimumab (40 mg)	81.8%	77.5%	85.2%	64.8%	59.0%	69.8%	38.9%	33.1%	44.2%	14.1%	11.0%	17.4%	8
Apremilast (30 mg)	46.7%	40.1%	53.1%	27.1%	21.8%	32.6%	10.2%	7.5%	13.3%	1.9%	1.3%	2.8%	11
Etanercept (50 mg/week)	54.7%	48.9%	60.2%	34.1%	28.9%	39.3%	14.2%	11.1%	17.5%	3.1%	2.2%	4.2%	10
Etanercept (100 mg/week)	66.7%	62.7%	70.1%	46.1%	41.9%	49.9%	22.4%	19.3%	25.3%	6.0%	4.8%	7.3%	9
Infliximab (5 mg/kg)	88.6%	85.3%	91.0%	75.0%	70.0%	79.2%	50.5%	44.5%	56.0%	21.8%	17.6%	26.1%	4
Ixekizumab (80 mg Q2W)	94.8%	93.2%	96.1%	86.4%	83.2%	89.2%	66.9%	61.8%	71.6%	36.1%	31.2%	41.2%	1
Secukinumab (300 mg)	90.4%	87.9%	92.5%	78.2%	74.0%	81.9%	54.6%	49.2%	59.8%	24.9%	20.8%	29.3%	3
Ustekinumab (45 mg)	82.0%	78.3%	85.1%	65.1%	60.0%	69.6%	39.2%	34.1%	44.0%	14.3%	11.5%	17.3%	7
Ustekinumab (90 mg)	84.0%	80.4%	87.1%	68.0%	62.8%	72.7%	42.3%	36.8%	47.6%	16.2%	12.9%	19.7%	5
Ustekinumab (in-label dose)	82.7%	78.5%	86.2%	66.0%	60.3%	71.3%	40.1%	34.4%	46.0%	14.9%	11.6%	18.6%	6
Dimethyl Fumarate	45.2%	33.7%	56.7%	25.8%	17.2%	35.9%	9.5%	5.4%	15.3%	1.8%	0.8%	3.5%	12
Synthesis model variant c. (baseline risk estimated from the AMAGINE 2 and 3 trials only)													
Placebo	16.8%	16.6%	16.9%	6.8%	6.5%	7.0%	1.6%	1.5%	1.7%	0.2%	0.1%	0.2%	13
Brodalumab (210 mg)	[redacted]												2

Adalimumab (40 mg)	85.6%	83.3%	87.7%	70.4%	66.9%	73.6%	45.0%	41.1%	48.8%	17.9%	15.4%	20.5%	8
Apremilast (30 mg)	53.0%	48.2%	57.7%	32.5%	28.3%	36.9%	13.2%	10.8%	15.9%	2.8%	2.1%	3.7%	11
Etanercept (50 mg/week)	60.8%	56.3%	65.4%	40.0%	35.6%	44.7%	18.0%	15.1%	21.3%	4.4%	3.4%	5.6%	10
Etanercept (100 mg/week)	72.1%	69.6%	74.7%	52.3%	49.4%	55.4%	27.3%	24.9%	29.9%	8.1%	7.0%	9.4%	9
Infliximab (5 mg/kg)	91.3%	89.1%	93.2%	79.7%	75.9%	83.2%	56.7%	51.7%	61.7%	26.6%	22.6%	31.1%	4
Ixekizumab (80 mg Q2W)	96.3%	95.2%	97.2%	89.6%	87.2%	91.6%	72.4%	68.2%	76.3%	42.1%	37.5%	46.9%	1
Secukinumab (300 mg)	92.8%	91.1%	94.4%	82.5%	79.3%	85.5%	60.7%	56.2%	65.3%	30.1%	26.2%	34.5%	3
Ustekinumab (45 mg)	85.8%	83.1%	88.2%	70.7%	66.6%	74.5%	45.3%	40.8%	49.8%	18.1%	15.2%	21.3%	7
Ustekinumab (90 mg)	87.5%	84.6%	90.1%	73.4%	68.9%	77.5%	48.5%	43.3%	53.7%	20.3%	16.8%	24.3%	5
Ustekinumab (in-label dose)	86.4%	83.5%	89.0%	71.5%	67.3%	75.7%	46.3%	41.5%	51.3%	18.8%	15.7%	22.4%	6
Dimethyl Fumarate	51.4%	41.5%	61.3%	31.1%	22.9%	40.4%	12.4%	8.0%	18.3%	2.6%	1.4%	4.5%	12

4.5 Conclusions of the clinical effectiveness section

The clinical evidence presented in the submission is based on three multicentre double-blind RCTs (AMAGINE-1, AMAGINE-2 and AMAGINE-3) comparing brodalumab to placebo and/or an active control of ustekinumab. An NMA was undertaken in order to compare brodalumab with the other therapies available at the same point in the treatment pathway, based on short-term efficacy data from individual trials.

All three of the AMAGINE trials were good quality RCTs and the results are likely to be reliable. Trial inclusion criteria appear to have been appropriate and baseline characteristics were similar across treatment groups. However, inclusion criteria relating to disease severity were not the same as the threshold specified in the NICE treatment pathway (PASI score ≥10 and DLQI score >10); the AMAGINE trials recruited patients with a higher PASI score (≥12) but did not specify a minimum DLQI score. In addition, 17-35% patients in the AMAGINE trials had not received previous systemic therapy or phototherapy, which is not consistent with the proposed positioning of brodalumab in the treatment pathway. The AMAGINE trials also excluded patients who had previously received ustekinumab or anti-IL-17 therapy, which may not be reflective of how brodalumab would be positioned in practice. Therefore, the results of the AMAGINE trials may not be entirely generalisable to the proposed eligible population.

The trials demonstrated that brodalumab 210mg Q2W significantly reduced the severity of psoriasis and its impact on health-related quality of life compared with placebo at week 12 [redacted]. The AMAGINE-2 and AMAGINE-3 trials demonstrated that patients taking brodalumab 210mg Q2W were statistically significantly more likely to achieve a PASI 100 response, PASI 90 response, sPGA score of 0 or 1, sPGA score of 0 and PSI response at 12 weeks than patients taking ustekinumab. In those patients who continually received brodalumab 210mg Q2W or ustekinumab throughout the study, PASI 75 and PASI 90 response rates were maintained to week 52, while PASI 100 response rates increased slightly. Improvements in DLQI score at 12 and 52 weeks were numerically greater with brodalumab compared with ustekinumab but statistical significance was not assessed. Data are not provided on the rate of patients with an initial response to treatment who later experienced a return of disease so it is not possible to know if all patients achieving these thresholds at week 12 maintained their response.

The results of the subgroup analyses demonstrate that brodalumab 210 mg Q2W was significantly more efficacious than placebo and ustekinumab regardless of disease severity or prior exposure to systemic therapy, phototherapy and biological therapy. Across the three AMAGINE trials withdrawal rates in patients treated with brodalumab were low with around 88% completing the study to week 52;

for patients receiving the 210 mg Q2W dose, 81-82% patients completed the study to week 52. The ERG notes this is comparable with the drug survival rates published for other biologics.

Across the AMAGINE trials adverse effects were fairly common but generally did not require treatment discontinuation. Injection site reactions (due to the mode of administration) and Candida infections were associated with brodalumab. Suicide and suicidal ideation has been raised as a potential concern with brodalumab but reviews by the company and the FDA have been unable to draw any firm conclusions regarding whether there is an increased risk associated with brodalumab.

The ERG considers the NMA to be appropriate to pool trial results and compare treatments available for moderate to severe plaque psoriasis. It appears to have included all relevant trials of brodalumab and other therapies and the patient characteristics and study design of the trials included appear similar enough to be pooled. The NMA results presented are the proportion of patients at the end of the study-defined induction period achieving each level of PASI response (PASI 50, PASI 75, PASI 90 and PASI 100) for each treatment, reflecting the economic model.

When ranked in order of effectiveness (median probability of achieving a PASI 75 response), the results for the base case NMA and sensitivity analyses are consistent: ixekizumab, brodalumab, secukinumab, infliximab, ustekinumab, adalimumab, etanercept, apremilast, DMF, placebo. Similarly, for PASI 50, PASI 90 and PASI 100 response, brodalumab had a higher probability of response than ustekinumab, adalimumab, etanercept, apremilast, DMF and placebo, and a similar probability of response to ixekizumab, secukinumab and infliximab. The results of the NMA, in terms of ranking order of effectiveness, were consistent with those of NMAs undertaken in other recent STAs of treatments for moderate to severe plaque psoriasis in adults and the NMA undertaken for the development of the BAD guidelines.

The considerable variation in PASI response rates in the placebo arms of the trials included in the NMA was explored in the company submission using NMA meta-regression models on baseline risk (i.e. placebo response). A comparison of unadjusted and adjusted models was reported, but the unadjusted model was chosen for the company base case. Predicted PASI responses from the ERG's revised placebo adjusted synthesis model were similar to those presented by the company, providing reassurance regarding the company analyses. The treatment rankings presented by the company were unaltered.

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 critical appraisal was conducted with the aid of a checklist (Appendix 10.2) to assess quality and a narrative review to highlight key assumptions and areas of uncertainty.

The economic submission included:

1. A description of two SLRs, of which one was performed to identify prior evidence on the cost-effectiveness of brodalumab and the other to identify evidence on the cost-effectiveness of comparator therapies (i.e. other biologic therapies, apremilast and DMF); CS section B.3.1, with details provided in Appendix G. A series of systematic reviews were also conducted to collect relevant evidence about utility values and mapping algorithms (CS section B.3.4.3, with details provided in Appendix H).

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

3. An electronic version of economic model developed in Microsoft Excel ®. A separate Excel spreadsheet was also provided which reported Markov and QALY traces.

In response to a number of points for clarification raised by the ERG, the company further submitted:

4. A response to the points for clarification, including supplementary results from the NMA, additional HRQoL analysis and disaggregated resource use and unit cost estimates applied to Best Supportive Case (BSC).

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

5.1.1 Searches

The company undertook two SLRs to identify published economic evaluations for individuals with moderate-to-severe plaque psoriasis. The first review aimed to identify economic evaluation studies including brodalumab to assess whether a *de novo* model should be developed. Anticipating this evidence to be sparse, a second SLR was undertaken to identify other published models evaluating a broader set of biologic and non-biologic interventions. Full details of the search strategies are presented in Appendix G of the company submission.

Both SLRs searched the following electronic databases: Medline®, Medline® In-Process (and other non-indexed citations), Embase, NHS EED (via The Cochrane Library), and EconLit. Additional evidence from the following congresses was also searched: ISPOR (both European and US conferences), World Congress of Dermatology, American Academy of Dermatology. The International Congress on Psoriasis, the European Academy of Dermatology and Venereology and the British Association of Dermatologists congresses are indexed within Embase. A supplementary search of the cost-effectiveness analysis (CEA) Registry and NICE Health Technology Assessment (HTA) website was also performed.

The electronic database searches were initially performed on 31st January 2017 and were later updated on 15th August 2017. Searches for other published models of therapies in psoriasis were limited to 2014 onwards, with the SLR presented in a previous NICE appraisal (TA350)[54] used to cover the period between 1998 and 2014. Supplementary congresses searches included the period from 2014 onwards. An English language limit was applied to both SLRs conducted by the company.

The ERG considers that thorough searches of appropriate databases and conference proceedings were undertaken. The structure of the search strategies was appropriate and the MEDLINE and Embase strategies incorporated a study design search filter to limit retrieval to economic studies of brodalumab. The strategies contained relevant subject headings, text word searches and synonyms and all search lines were combined correctly.

5.1.2 Inclusion/exclusion criteria used for study selection

The inclusion and exclusion criteria are provided in Table 107 and 108 of Appendix G, and presented in Tables 5.1 and 5.2 of the company submission.

5.1.3 Studies included and excluded in the cost effectiveness review

The initial search of economic evaluations of brodalumab identified 14 studies. 3 of these studies were duplicates, leaving 11 publications being assessed against the inclusion/exclusion criteria, in a double-blind manner. No study met the inclusion criteria and no further studies were identified with the supplementary searches. However, the update search subsequently identified one publication which passed double-blinded screening against the inclusion criteria.

The broader search identified 540 publications. After duplicates were removed, 441 abstracts were screened and 385 of these excluded, leaving 56 full text papers to be assessed. 41 of those did not meet inclusion criteria, leaving 15 studies to be included in the final review. Four of these studies were UK based. The update search identified further 77 studies, of which 15 were excluded being duplicates. 53 of the 62 remaining abstracts did not meet inclusion criteria, leaving 8 full text papers

to be assessed for eligibility. Evidence from supplementary searches (NICE website, hand searches) identified 8 additional studies, of which 7 were previous NICE TAs.

The only publication identified assessing the cost-effectiveness of brodalumab was a modelling study by the US Institute for Clinical and Economic Review. The US study compared immunomodulators (including brodalumab) with non-targeted therapy in adult patients with moderate-to-severe psoriasis and who had already failed topical treatment, systemic therapy, or phototherapy. The model structure is broadly in line with the model used in the CS and results were presented as the incremental cost per QALY (expressed in US $). As pricing for brodalumab was not available at the time the study was published, the average of WAC (wholesale acquisition price) for ixekizumab and secukinumab was used, with a further 40% discount applied. A summary of the study is presented in Table 39 of the CS.

The SLR for any psoriasis therapy identified 44 studies, of which 7 were UK based and were described and critically appraised. Previous NICE TAs were summarised in section B.3.2.4 (Table 41, page 104-108) of the CS.

5.1.4 Conclusions of the cost effectiveness review

The company's search identified a single published cost-effectiveness study of brodalumab. The study was undertaken prior to the EU marketing authorisation and assumptions were made in relation to the potential acquisition cost. Given this limitation and issues regarding the generalisability of a US setting, the ERG considers that the de-novo cost-effectiveness analysis reported in the company submission to be the most relevant source of evidence to inform the decision problem.

The critical appraisal of the broader set of studies was largely a description of the models' general features rather than a thorough analysis of the various modelling approaches, key assumptions, and data sources. However, the review provided useful contextual information and allowed the company to identify and justify any important differences in approaches.

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 12. The results of the checklist used to assess the quality of the submission are reported in Appendix 10.2.

Table 12: Summary of the company's economic evaluation

Element of HTA	Approach	Source/Justification	Location in CS
Model Structure	A Markov model was employed for the cost-effectiveness analysis	The use of a Markov model structure is appropriate when modelling sequences of treatments over an appropriate time horizon	Section B.3.2.2 (p.109), Table 41 (p. 112)
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.	The company proposed that brodalumab will be used in line with the existing NICE pathway, which positions biologics for use after systemic non-biological therapies	Section B.3.2.1 (p. 109)
Intervention and comparators	Different treatment sequences were considered, consisting of three lines of biologic treatment followed by BSC: 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 –	The comparators included in the model correspond to those recommended by NICE for the treatment of psoriasis after systemic non-biologic therapy has failed or was not tolerated. Although infliximab is recommended for severe patients only, it was included in the base-case on the basis of completeness. The positioning of biologics in the sequence was informed by the 2017 BAD guidelines, the CCG guidance on treatment sequencing in psoriasis and expert opinion from the company's advisory group.	Sections B.3.2.4 (p. 111) and B.3.2.5 (p. 116)

	Secukinumab – BSC 8. Secukinumab – Ustekinumab – Adalimumab – BSC 9. Ustekinumab – Adalimumab – Secukinumab – BSC		
Perspective, time horizon and discounting	NHS and PSS perspective. A time horizon of 40 years was chosen and a discount rate of 3.5% was applied to both costs and QALYs	The perspective and discounting were considered consistent with the NICE reference case. A 40-year horizon was considered sufficiently long to capture the incremental costs and benefits associated with the treatment sequence.	Section B.3.2.3 (p.111), Table 41 (p. 112)
Treatment effectiveness and extrapolation	Results from the NMA were used to inform the probability of response to treatment, by PASI category (0-49, 50-74, 75-89, 90-99, 100), during the induction period of each treatment. 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.	Results from the NMA ensure all available evidence on the response to treatments is considered, addressing the lack of head-to-head trials comparing brodalumab with drugs other than ustekinumab. The same constant annual discontinuation rate was applied to all drugs and was justified as being consistent with assumptions in previous NICE TAs. The discontinuation rate was derived from a UK-based registry (BADBIR) and the approach used to estimate the annual rate was stated to have been validated by an advisory board.	Section B.2.3.6 (p. 117) and B.3.3 (p. 119-120)
Health-related quality of life	Estimated based on EQ-5D-3L data collected in the AMAGINE-1 trial.	The company justifies the use of EQ-5D data from AMAGINE-1 as providing the most relevant	Section B.3.4 (page 123-126),

(HRQoL)	An ANOVA regression was used to identify the relationship between change in EQ-5D, PASI response at week 12, and baseline DLQI. The base-case considered the subgroup with DLQI>10 only.	and robust source of utility data for brodalumab. The use of the DLQI>10 subgroup is in line with the definition of moderate-to-severe psoriasis as described in the NICE Clinical Guideline.	Table 41 (p.113)
Resources and Costs	Costs and healthcare resource use considered included: • Drug Acquisition • Administration • Monitoring • Adverse Events • BSC	The identification and evaluation of resource use was justified as being consistent with previous NICE appraisals and current clinical guidelines.	Section B.3.5, Table 41 (p. 113)
Adverse events	Adverse events, considered to have a large impact on costs, were included in the analysis. Impact of adverse events on HRQoL was explored by applying a utility multiplier for serious infection. The impact of non-malignant skin cancer (NMSC), malignances other than NMSC and major adverse cardiovascular events (MACE) on costs were included in a scenario analysis	Unit costs for adverse events were collected from NHS reference costs. Incidence of the adverse events included was collected from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) study and other long-term RCTs (CLEAR, IXORA-S, AMAGINE-2 and -3) Inclusion of the impact of adverse events on both costs and HRQoL was justified on the basis of data availability.	Section B.3.3.1 (p. 120) and Table 55 (p. 132) for costs. Section B.3.4.3 (p. 127) for impact on HRQoL. Table 41 (p. 113)
Best Supportive Care	Cost of BSC was based on Fonia et al. (2010) The effectiveness of BSC was assumed to be the same as the placebo arm of the NMA.	Fonia et al. (2010) was justified as being consistent with the source use in recent NICE appraisals.	Section B.3.5.1 (p.131) for costs and Section B.3.3.1 (p.118) for effectiveness
Subgroups	No clinically defined subgroup	As treatment response was	Section B.3.9

	analysis is reported in the CS	reported to be consistent across clinically defined subgroups (previous use of systemic therapy, phototherapy and biological therapy, and disease severity), the company chose not to perform any subgroup analysis	(p.157)
Sensitivity analysis	The company performed both one-way and probabilistic sensitivity analysis. A series of scenarios using alternative assumptions on key inputs were also presented	Justified based on the NICE reference case and the current methods guide.	Section B.3.8

5.2.1 NICE reference case checklist

The NICE reference case checklist is given in Table 13.

Table 13: NICE reference case checklist

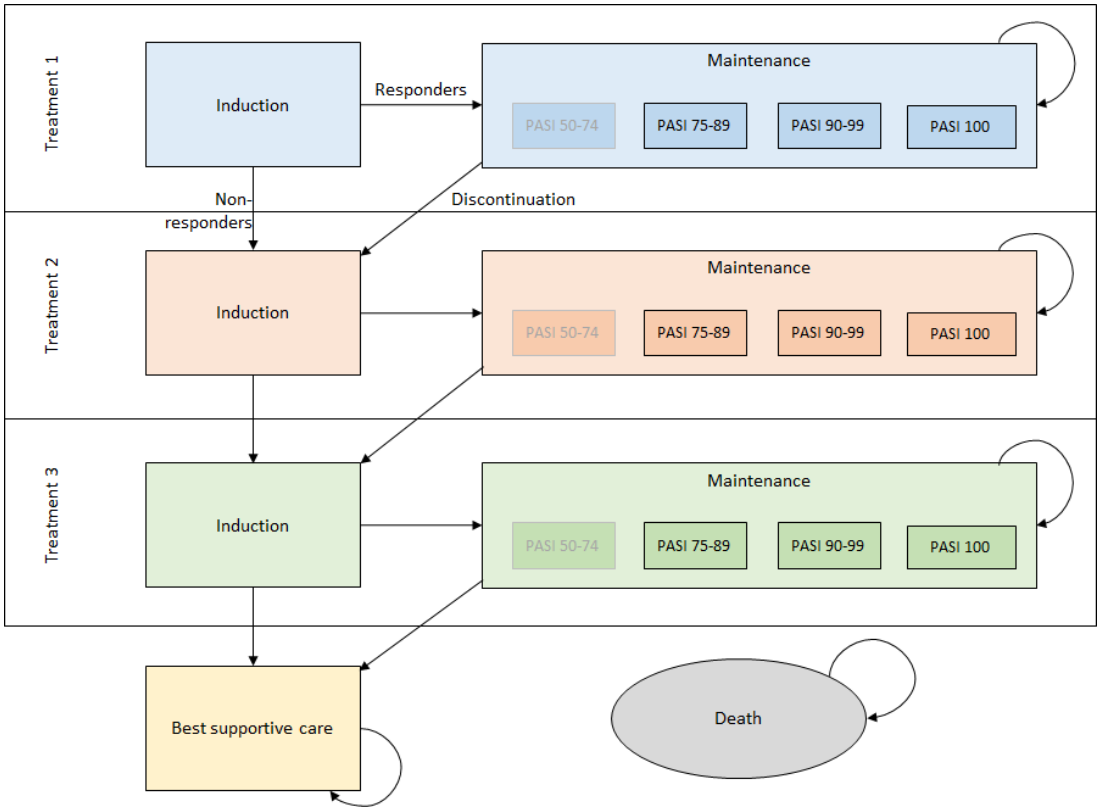
Element of economic evaluation	**NICE Reference Case**	**Included in submission**	**Comment on whether *de novo* evaluation meets requirements of NICE reference case**
Defining the decision problem	As per NICE scope	Partially	The NICE scope refers to "*adults with moderate-to-severe plaque psoriasis"*, 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, who are candidates for systemic therapy, for which standard systemic therapies have failed or are not tolerated/contraindicated. Therefore, the company positions brodalumab together with other systemic biologic therapies, anticipating it will be used at a similar point to the current NICE pathway for other biologic therapies, DMF and apremilast.
Comparator(s)	As listed in the scope developed by NICE	Partially	The company states that the most appropriate comparators for brodalumab, given its proposed positioning are other biologic therapies, DMF and apremilast. Therefore, other non-biologic systemic therapies, although included in the NICE scope, were not considered as relevant comparators. A restricted set of 'all feasible' sequences were compared. Brodalumab 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	
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 time horizon of 40 years, which is considered sufficiently long to account for all important differences between the comparator sequences.

Element of economic evaluation	**NICE Reference Case**	**Included in submission**	**Comment on whether *de novo* evaluation meets requirements of NICE reference case**
Synthesis of evidence on health effect	Based on systematic review	Yes	A systematic review was undertaken to collect all available evidence on relevant health effects from published studies and previous submissions.
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 AMAGINE-1 trial
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes	Utilities were calculated using UK preference weights for EQ-5D-3L
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 brodalumab 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 appropriately model treatment sequences over an appropriate time horizon. The ERG notes that the model structure is consistent with the most recent NICE TA appraisals which have assessed treatment sequences.

Figure 6: Schematic model diagram from CS (CS Figure 29)



The model consists of four treatment-related health states (induction, maintenance, best supportive care and death) with patients being allocated to one of five PASI response categories (PASI 0-49, PASI 50-74, PASI 75-89, PASI 90-99 and PASI 100).

Each line of treatment in a sequence starts with an induction period lasting between 10 and 16 weeks. At the end of the induction period, individuals are assigned to one of the five PASI response categories based on the NMA results. Individuals who achieve a response of PASI≥75 (considered as "adequate" according to NICE CG153) are assumed to continue with the same treatment and enter the maintenance phase of the model. Individuals who achieve PASI≤50 are assumed to discontinue their treatment and then switch to the next treatment in the sequence.

During the maintenance period, individuals are assumed to continue to receive the same treatment and maintain the same PASI response until the treatment is discontinued due to loss of response and/or

adverse events. In line with previous economic evaluations and all NICE Technology Appraisals (TAs), the company base-case assumes that individuals discontinue treatment at a constant annual rate.

When a treatment is discontinued, individuals are assumed to revert back to their PASI baseline score before starting a new treatment. 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 assumed to comprise of a bundle of non-biologic supportive therapies. Upon entry to the BSC state, patients are assumed to remain in this state until the end of the model time horizon or death. A separate and common transition to death is assumed from all states.

Table 14: Summary of Model States

State	Definition
Induction Period	10-16 weeks (depending on the treatment), after which treatment response is assessed for all patients.
Maintenance Period	Continued use of treatment if response is ≥PASI 75 at the end of the induction period.
BSC	Last treatment strategy for patients having failed all other treatment options.
Death	Absorbing state which can be reached from any state and at any time.

The model assumes that the assessment of response will occur at 12-weeks for brodalumab. The SPC for brodalumab states that '*consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks*'. The company justified a 12-week response period on the basis that this was consistent with the timing of the response assessments in the AMAGINE trial programme.

The ERG considers a 12-week response assessment period for brodalumab to be appropriate. This period is also consistent with the assessment periods recommended by NICE for the targeted IL-I7A inhibitors, secukinumab and ixekizumab (TA350 and TA442).[46, 54]

A summary of the response assessment periods for brodalumab and other comparators is provided in Table 15.

Table 15: Summary of response assessment periods

Drug	**Duration**	**Source**
Brodalumab	12 weeks	Company assumption and

		SPC
Adalimumab	16 weeks	NICE TA 455[55]
Apremilast	16 weeks	NICE TA 368[56]
Dimethyl fumarate	16 weeks	NICE TA 475[47]
Etanercept	12 weeks	NICE TA 103[57]
Infliximab	10 weeks	NICE TA 134[58]
Ixekizumab	12 weeks	NICE TA 442[46]
Secukinumab	12 weeks	NICE TA 350[54]
Ustekinumab	16 weeks	NICE TA 180[59]

To account for the different assessment periods recommended by NICE for the initial response assessment, the model uses a cycle length of 2-weeks. The cycle length was considered sufficiently short that no half-cycle correction was deemed necessary by the company.

The ERG considers that a 2-week cycle length is appropriate and the lack of a half-cycle correction is unlikely to make a material difference to the incremental calculations.

5.2.3 Population

Brodalumab is indicated "*for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy"* (CS, p.110). However, the CS proposed a more restrictive positioning for brodalumab alongside other biologic therapies recommended within the current NICE treatment pathway. 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.

Although the population considered in the CS is more restrictive than the product license 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 assessments for other biologic treatments. The focus on this subpopulation in previous NICE appraisals stems largely from existing clinical guidelines and criteria for commencing biologic treatments, as opposed to reflecting important differences in the licenses of the alternative biologic treatments.

Patients entering the model are assumed to be similar to the average baseline characteristics reported across the NMA studies. The mean age and weight of the cohort were assumed to be 45 years and 85.8kg, respectively. Approximately two-thirds (68%) of cohort were assumed to be male.

The model characteristics appear reasonably consistent with the baseline characteristics of patients included in the AMAGINE trials (Table 16).

Table 16: Baseline characteristics from the AMAGINE Trials (from Table 10 of CS)

Study	% Male	Mean Age (years + SD)	Mean weight (kg) , ± SD	Psoriasis Duration (years + SD)	PASI Score (SD)
AMAGINE 1	73	47 ± 13	91.4 ± 23.4	21 ± 12	19.7 ± 7.7
AMAGINE 2	71	44 ± 13	91± 23	18 ± 12	20.4 ± 8.2
AMAGINE 3	66	44 ± 13	90 ± 23	18 ± 12	20.1 ± 8.7

5.2.4 Interventions and comparators

The model includes a total of nine treatment sequences which include three lines of active therapy, followed by BSC (see Table 17 below). Brodalumab 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 including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or who are intolerant or have a contraindication to these treatments.

The comparator list includes: adalimumab; apremilast; dimethyl fumerate (DMF); etanercept; infliximab; ixekizumab; secukinumab and ustekinumab. Although infliximab is only recommended by NICE for patients with very severe psoriasis (defined as PASI ≥20 and DLQI>18), the company included infliximab within their base case for completeness.

Brodalumab and each comparator treatment are then assumed to be followed by a second and a third line biologic therapy. Where possible, second- and third-line biologic therapies were selected by the company based on a different mechanism of action to the preceding line. The treatments included as second and third line were also stated to be based on the 2017 BAD guidelines, Clinical Commissioning Group guidance, market share data and clinical advice. Accordingly, the company assumed that ustekinumab and secukinumab were likely to be the most commonly used second and third-line treatments, respectively. A separate sensitivity analysis also considered infliximab as an alternative third-line treatment, consistent with the assumptions and sequences evaluated in the previous STA appraisal of ixezikumab (TA442).[46]

Table 17: Treatment sequences compared in the company base-case (CS Table 43)

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

The company acknowledges that several modelling alternatives could have been chosen when constructing the comparator sequences, but that priority was given to the ease of comparability with the comparators included in the NICE scope. This meant, for example, maintaining a common second- and third-line treatment across sequences as opposed to including all possible treatment combinations.

The ERG notes 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 the most recent NICE appraisals (e.g. TA368, TA442 and TA475). However, the ERG also notes that previous appraisals have also raised questions regarding whether the selected sequences (excluding a new therapy) are representative of current clinical practice and whether different positions have been assessed for a new therapy. Concerns have also 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, particularly if there are treatments included in a sequence which are not cost-effective themselves (e.g. TA442 and TA475).

The ERG considers that the results presented by the company have been appropriately justified but are clearly partial in terms of the sequences and positions evaluated. The ERG acknowledges the challenges of including all feasible sequences (which include sequences of different lengths and different ordering) and understands the rationale and basis for the sequences included by the company. However, the ERG does not consider that the concerns raised in previous NICE appraisals have been fully addressed by the company.

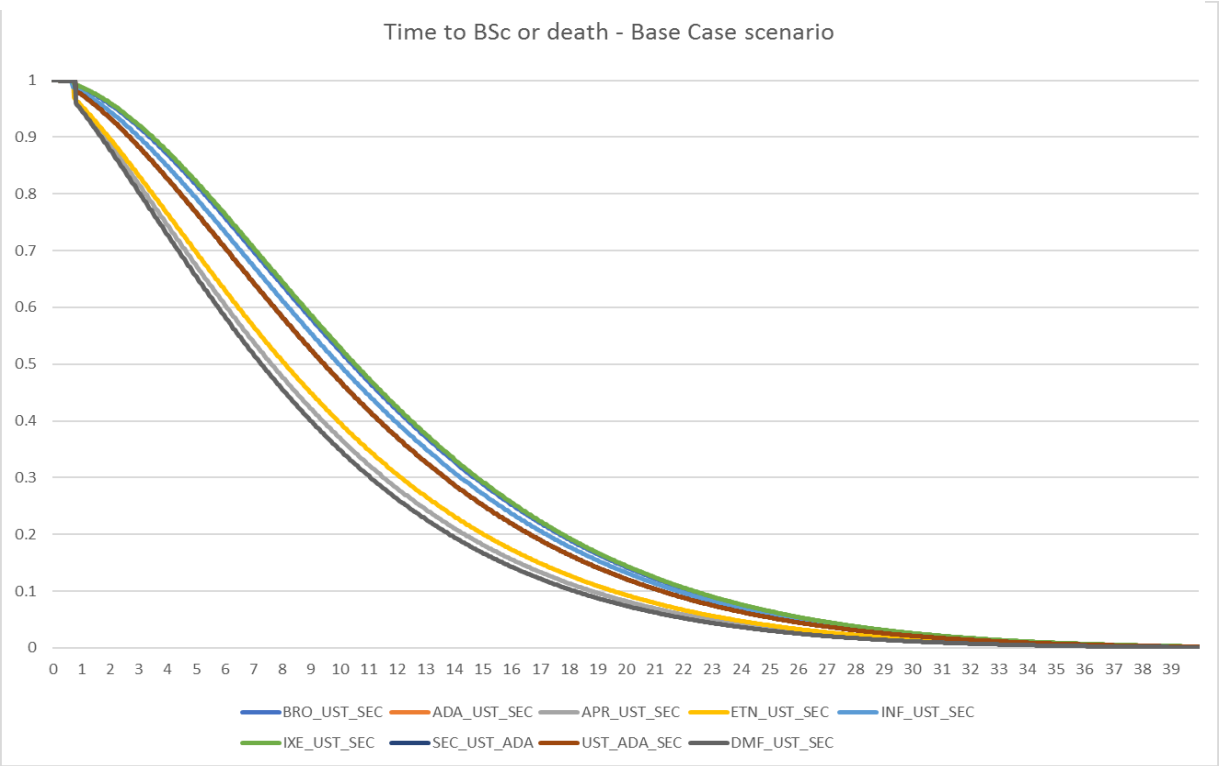
In Section 5.3.1, the ERG proposes an alternative approach to inform the cost-effectiveness of alternative sequences based on net-benefit calculations and associated rankings of each individual treatment compared to BSC.

5.2.5 Perspective, time horizon and discounting

The perspective of the analysis was the NHS and Personal Social Services. An annual discount rate of 3.5% was applied to both costs and health effects, in line with NICE guidance. A time horizon of 40 years was chosen as it was considered sufficient to capture all relevant differences in costs and benefits between comparators. The impact of a shorter 10-year time horizon, in line with several previous NICE TAs, was also explored in a scenario analysis.

The use of a 40 year time horizon was considered to be appropriate by the ERG. As Figure 77 shows, the differences between the sequences in terms of the time to BSC or death are still evident at 10-years and a longer horizon is needed to fully capture differences in longer term outcomes and costs. The figure also shows that by 40-years, the curves appear to have completely converged, further supporting the choice of time horizon.

Figure 7: Time to BSC or Death



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 relative to baseline. Relative change in PASI response 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 unadjusted NMA described and critiqued in previous sections.

At the end of each induction period patients are allocated to one of the following five 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 90-99: an improvement in their psoriasis between 90 and 99%
- PASI 100: an improvement in their psoriasis of 100%, i.e. total clearance

The proportion of patients in each PASI category at the end of the induction period are summarised in Table 18. The placebo responses from the NMA were used to define PASI response categories for

patients in the BSC state. Uncertainty in the predicted response rates from the NMA was reflected in the model by directly exporting the simulated posterior distributions, preserving any correlations in the data.

Table 18: Proportion of patients in each PASI response category at the end of the induction period (CS Table 44)

Treatment	Induction period duration (weeks)	Treatment effect estimate (SE)[a,b]	PASI 0–49	PASI 50–74	PASI 75–89	PASI 90–99	PASI 100
Brodalumab	12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	16	–1.99 (0.07)	0.17	0.17	0.26	0.25	0.15
Apremilast	16	–0.97 (0.08)	0.53	0.20	0.17	0.08	0.02
Dimethyl fumarate	16	–0.71 (0.16)	0.63	0.17	0.13	0.05	0.01
Etanercept 50 mg / week	12	–1.3 (0.07)	0.40	0.20	0.21	0.14	0.05
Infliximab	10	–2.39 (0.09)	0.09	0.12	0.23	0.30	0.26
Ixekizumab	12	–2.88 (0.07)	0.03	0.06	0.17	0.30	0.44
Secukinumab	12	–2.56 (0.07)	0.07	0.10	0.21	0.31	0.32
Ustekinumab	16	–2.13 (0.07)	0.14	0.15	0.25	0.27	0.18
BSC	NA	0 (NA)	0.85	0.09	0.04	0.01	0.00

In the base case analysis, 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 PASI 75 was "*the most commonly used primary measure of effectiveness in clinical trials and has been employed in all previous NICE TAs as the only base-case response criterion for treatment continuation*" (CS, p. 118). The impact of using PASI 50 as an alternative cut-off was explored in a scenario analysis. This scenario was presented as a proxy for the NICE CG153 and BAD guidelines response definition of PASI 75 or PASI 50 and a 5-point decrease in DLQI.

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. The company justified this approach by claiming that the evidence was insufficient to perform a robust NMA due to the absence of subgroup data routinely reported across the comparator trials. Also, no significant differences were reported by the company when comparing biologic-naïve and biologic-experienced patients from the AMAGINE trials. A scenario analysis explored the impact of reducing effectiveness for biologic-experienced patients in the induction period only, in the maintenance period only, or in both.

Responders to treatment during the induction period were assumed to maintain their level of response during the maintenance phase until treatment discontinuation. The rate of discontinuation was

informed by a recent study on the long-term drug survival rates of four biologics (adalimumab, etanercept, infliximab and ustekinumab) from the UK BADBIR audit of 3,523 biologic naïve adult patients.[21]

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.). The discontinuation rate was obtained by applying an exponential model to data from BADBIR using data from years 2 and 3. The company justified excluding the year 1 data to avoid potential double counting of discontinuations due to early non-response.

The ERG considers the company's approach to discontinuation rates in the base-case to be reasonable and generally consistent with previous appraisals. Although the discontinuation rate applied in the base-case is lower than in previous submissions (18.7% vs 20%), the difference is marginal. The difference appears to relate to the exclusion of first year discontinuation data from BADBIR. This is justified by the company to avoid double counting of discontinuation due to primary non response already accounted for in the model structure. The ERG considers that this approach to be reasonable.

The discontinuation rate was differentiated by treatment class in a separate scenario analysis. The company argued that using a common discontinuation rate across all treatments may represent a conservative assumption for brodalumab. The company highlighted that the BADBIR registry reported a lower rate of discontinuation with ustekinumab compared with anti-TNF therapies (adalimumab, etanercept and infliximab). The scenario analysis explored the assumption that the evidence for ustekinumab might be generalised to a class effect applying to all the IL-inhibitors (i.e. brodalumab, ixekizumab, secukinumab and ustekinumab). The company proceeded to estimate separate discontinuation rates based on drug class using a separate exponential model fitted to the anti-TNF data and applying a hazard ratio (HR) reported by Warren et al (2015) from BADBIR for ustekinumab (HR = 0.48, 95% CI 0.37-0.62). The HR was used to estimate the equivalent discontinuation rate for the IL-inhibitors.[21]

In the scenario analysis, the company used data for adalimumab reported in BADBIR. This was reported to be the most commonly used anti-TNF therapy and the discontinuation rate for adalimumab was assumed to be representative of all the anti-TNFs therapies. In the absence of equivalent data from BADBIR for DMF and apremilast, the same discontinuation rate was assumed as for the anti-TNFs therapies. The resulting discontinuation rates were 14.7% for the anti-TNF therapies (and DMF and apremilast) and 7.3% for all the IL-inhibitors.

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

- The discontinuation rates applied in the scenario (14.7% and 7.3%) are lower for all therapies compared to the base case rate of 18.7%. Hence, the assumptions being made across the base-case case and scenario analysis appear to be inconsistent. This inconsistency appears to stem from the assumption that the discontinuation rate of adalimumab is representative of all anti-TNF therapies. However, the lower rate of 14.7% evident in the adalimumab data may also indicate potential differences within the anti-TNF class. Indeed, the data from BADBIR shows that adalimumab had the highest drug survival (i.e. lowest discontinuation rate) amongst the anti-TNF therapies in biologic-naïve patients. [21]

- Given that differences between therapies may exist within the anti-TNF class, 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.

- The HR for utsekinumab appears to be based on the entire follow-up and hence does not appear to distinguish between discontinuation due to a lack of treatment response in the short-term, i.e. during the initial trial period, and the long-term for patients who are responders to treatment. Therefore, the differences in withdrawal rates by treatment may reflect the higher initial efficacy of ustekinumab compared to adalimumab and etanercept, rather than reflecting differences between the treatments conditional on PASI75 response at the initial assessment point.

The ERG considers that the assumptions applied in the base case analysis appear more justifiable than those considered by the scenario. However, the ERG recognises that there exists significant uncertainty concerns both the rate itself and whether there are important treatment or class specific differences.

5.2.7 Health related quality of life (HRQoL)

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 (UK tariffs applied) collected in the AMAGINE-1 trial of brodalumab Q2W versus placebo.

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. Therefore, PASI response rates from the NMA are assumed to be a perfect proxy for HRQoL differences between treatments.

An analysis of variance (ANOVA) model, controlling for PASI response and baseline DLQI, was used to quantify the extent to which PASI response category affected change from baseline utility in the AMAGINE-1 study. The base-case analysis only included individuals with a baseline DLQI>10

(n=401) to be consistent with the definition of moderate-to-severe psoriasis as outlined in NICE CG153. The ERG notes that the approach to informing utilities is not consistent with the use of the ITT population from the NMA which is used to estimate PASI responses. However, a similar approach has been used in recent NICE appraisals and has been considered to be appropriate.

Table 19 summarises the utility values for the DLQI>10 population (base case assumption) and for all patients. The values show lower baseline utility values in the DLQI>10 population and higher increments for each PASI response category.

Table 19: Summary of utility values – DLQI>10 and all patients

State	Utility value: DLQI>10 (base case)	Utility value: All patients
Baseline	0.5206	0.6105
PASI < 50	(0.0158)	(0.0044)
PASI 50–74	(0.1898)	(0.1349)
PASI 75–89	(0.2946)	(0.2441)
PASI 90–99	(0.3552)	(0.2798)
PASI 100	(0.3680)	(0.2897)

Figures in brackets are increments which are applied to the baseline EQ-5D values

A utility multiplier obtained from the literature (0.9858) was used to adjust the utility value in the event of serious infection (the only adverse event considered in the base case). Due to their low incidence, additional adverse events (e.g. MACE) were included in a scenario analysis only, but their impact on HRQoL was not considered. The company also presented a separate scenario exploring the impact of using utility values derived from all patients. Other scenarios considered the application of utility values identified from external literature and previous NICE appraisals.

The ERG considers that the approach met the NICE reference case but notes that no adjustment has been made for the impact of ageing in the model. However, in the absence of any differential mortality effect assumed between treatments, the ERG does not consider that this introduces any potential bias when comparing alternative sequences of equal length.

The ERG also considers the use of the regression model to be appropriate for the purposes of informing the model. However, the submission did not adequately justify the use of a complete-case analysis or provide a rationale for only controlling for differences in baseline DLQI and not for other baseline covariates (e.g. baseline EQ-5D). Consequently, the ERG requested additional justification for these aspects as well as requests for alternative specifications of the ANOVA model and associated measures of goodness of fit.

As part of their response, the company provided additional information comparing complete case and multiple imputation analysis and summaries of the following alternative specifications of the EQ-5D regression model:

a) EQ-5D regression model adjusted for baseline EQ-5D score;

b) EQ-5D regression model adjusted for baseline EQ-5D score and baseline PASI, with and without adjustment for baseline DLQI; and

c) The above specifications for the subgroup with a baseline DLQI > 10.

The ERG was satisfied with the additional data submitted regarding the extent of missing data and the comparison of the results of a complete-case versus multiple imputation analysis. The extent of missing data appeared low (6.1% across all subjects) and differences between the analyses appeared minor. While the ERG would have preferred to see an analysis using multiple-imputation and taking into account within-patient correlation using repeated measures, the approach employed by the company seems unlikely to generate any important bias.

The company provided additional justification for adjusting for baseline DLQI, stating that this was done to align their approach with previous NICE TA submissions. The ERG has two main concerns regarding the specification of the regression model:

(i) There appears variability across previous submissions regarding which baseline covariates have been controlled for. However, several previous submissions appear to have controlled for baseline EQ-5D.

(ii) The ERG considers that a more appropriate consideration is the performance of alternative specifications and associated goodness of fit, rather than consistency with previous NICE TA approaches.

The company provided a comparison of the parameter coefficients and goodness of fit for three alternative ANOVA models, including the following alternative covariates: (i) baseline EQ-5D only, (ii) baseline EQ-5D and PASI and (iii) baseline EQ-5D, PASI and DLQI. These were reported and discussed in detail by the company in the response to clarification document.

The results from these alternative models showed that the model including baseline EQ-5D only consistently performed better in terms of goodness of fit across a range of measures (e.g. AIC, BIC etc). The ERG concludes that the regression model adjusting for baseline EQ-5D to be the most appropriate regression model presented by the company.

Table 20 summarises the utility values from the regression model adjusting for baseline EQ-5D only. The ERG notes that these results are consistent with the company base case results (adjusting for baseline DLQI only).

Table 20: Summary of utility values - DLQI>10 and all patients (adjusting for baseline EQ-5D)

State	Utility value: DLQI>10	Utility value: All patients
Baseline	0.5206	0.6105
PASI < 50	(0.0035)	(-0.0037)
PASI 50–74	(0.2337)	(0.1574)
PASI 75–89	(0.3411)	(0.2631)
PASI 90–99	(0.3608)	(0.2895)
PASI 100	(0.3774)	(0.2986)

Figures in brackets are increments which are applied to the baseline EQ-5D values

The ERG also notes that there exists uncertainty regarding whether EQ-5D data from the AMAGINE-1 trial can be generalised to the AMAGINE-2 and AMAGINE-3 trials which didn't collect EQ-5D data. The ERG has previously highlighted important differences in the rate of prior biologic use and differences in the baseline placebo rates between the AMAGINE-1 and AMAGINE-2 and 3 trials. It is unclear whether these differences might also affect the generalisability of the EQ-5D results.

To explore this issue further, the ERG requested additional comparisons across the separate AMAGINE trials based on mapping between DLQI and EQ-5D-3L. Although the mapped utility estimates are not considered directly exchangeable with the EQ-5D-3L values reported from AMAGINE-1, the ERG considered that being able to show consistency across the separate studies and populations based on the mapped values would provide additional reassurance regarding the generalisability of the values from the single trial which included the EQ-5D-3L instrument.

The company provided extensive additional results both for the subgroup with DLQI>10 and for all patients using 3 alternative mapping functions. These were reported and discussed in detail by the company in the response to clarification document. In summary, as expected, the company found differences in the predicted EQ-5D-3L values across the alternative mapping functions. More importantly, however, the results demonstrated consistent estimates within each mapping function for each PASI category across each of the separate AMAGINE trials. The ERG concurs with the

company's interpretation of these additional analyses and considers that the results of these analyses provide sufficient reassurance to believe that the EQ-5D-3L data reported in AMAGINE-1 can be generalised to the other AMAGINE trials.

The ERG would also like to acknowledge the extensive additional work that the company undertook to respond to these requests. These analyses have provided important confirmatory data supporting the generalisability of the values derived from the AMAGINE-1 trial. The ERG also notes that the utility increments for each response category based on EQ-5D-3L, based both on the company base-case regression and the ERG's preferred regression approach, lie within the range of the values for these increments based on the DLQI mapped values.

A systematic literature review was also undertaken by the company to identify evidence for utility values reported in the published literature and used in previous NICE appraisals. The ERG considers that the company searches were comprehensive and the structure of the search strategies was appropriate. The utility values identified by the company are summarised in Table 48 (p125) of the CS.

The company concluded that the values from AMAGINE-1 lie within the range of estimates identified from the SLR and previous NICE appraisals. The ERG notes, however, that drawing robust conclusions from these comparisons is challenging given the heterogeneity in the different approaches and regressions used (e.g. mapping vs directly reported EQ-5D data, EQ-5D-3L vs EQ-5D-5L etc). Given this heterogeneity, the ERG considers that a more restrictive comparison between the utility values reported for the alternative IL-17 treatments (brodalumab, secukinumab and ixekizumab) might provide an important additional point of reference.

Table 21 provides a comparison of utility values for brodalumab reported in the company submission and values sourced by the ERG from TA350 (secukinumab) and TA442 (ixekizumab).[46, 54]

The increments sourced by the ERG are consistent with those reported in the summary provided by the company. The only difference is that the company summary states that the baseline utility values were not reported for these TAs. The ERG sourced the baseline values from the company submission (TA350) and a recent related publication by Pickard et al (2017).[60]

Table 21: Comparison of utility values for the IL-17 therapies

	Brodalumab		**Secukinumab**	**Ixekizumab**	
	EQ-5D-3L		**EQ-5D-3L**	**EQ-5D-5L**	
	(n=621)		**(n=3,286)**	**(n=2,085)**	
	Company submission		**TA350**	**TA442**	**Pickard (2017)**
State	**Company base-case: DLQI>10**	**ERG preferred: DLQI>10**	**DLQI>10**	**DLQI>10**	**DLQI>10 (EQ-5D-3L cross walk)**
Baseline	0.5206	0.5206	0.6402	0.761*	0.660
PASI < 50	(0.0158)	(0.0035)	(0.109)	(0.0123)	(0.029)
PASI 50–74	(0.1898)	(0.2337)	(0.193)	(0.100)	(0.125)
PASI 75–89	(0.2946)	(0.3411)	(0.226)	(0.131)	(0.166)
PASI 90–99	(0.3552)	(0.3608)	NR	(0.144)	(0.184)
PASI 100	(0.3680)	(0.3774)	NR	(0.153)	(0.189)

Figures in brackets are increments which are applied to the baseline EQ-5D values. NB: values were only presented for secukinumab for PASI 90-100: (0.264); * reported in Pickard et al (2017)[60]

A number of important differences are evident across these separate sources which warrant further consideration. Firstly, there are differences in the instrument used to derive the utility values. Both the current submission and TA350 (secukinumab) used EQ-5D-3L (UK tariffs), whereas utility values for TA442 (ixekizumab) were based on EQ-5D-5L (provisional tariffs for England).

Importantly, TA442 was undertaken prior to the recent interim position statement made by NICE concerning the use of the 5 level version of the EQ-5D. This interim statement issued on August 11th 2017, recommends that:

- The 3 level version (EQ-5D-3L) and the UK Time-Trade Off (TTO) value set are (still) the reference case for HTA submission
- If the 5 level is used (EQ-5D-5L), then apply the mapping function developed by van Hout et al. (2012)[61] to convert it to the EQ-5D-3L for the reference-case analyses.

This is potentially an important consideration since the baseline utility value reported in TA442 is considerably higher and the increments for the PASI response categories much lower than those presented in the company submission and in TA350. However, since the values in TA442 do not appear to meet the requirements of the current NICE reference case, direct comparisons may not be appropriate.

The ERG identified a recent publication by Pickard et al (2017) which reported values for ixekizumab based on the mapping function recommended by NICE if the 5 level is used.[60] These values appear to meet the interim statement and hence may provide a more appropriate basis for comparison than the estimates reported in TA442. These values are included in Table 21 and are referred to as EQ-5D-3L cross-walk values.

Interestingly, the baseline utility values reported in TA350 and Pickard et al (2017) appear broadly comparable (ranging between 0.64 and 0.66) but also appear higher than the baseline utility reported in the current submission for brodalumab (0.52). This may indicate important differences in the trial populations, with individuals in the brodalumab trials appearing more severe in terms of their HRQoL impairment at baseline. Identifying systematic differences between the trials are problematic since the EQ-5D data being compared are from the subgroups of individuals with DLQI>10. In the absence of detailed information on the baseline characteristics across the studies for the DLQI>10 population, the ERG cannot determine the reason for these differences.

The different baseline utility values are also a potentially important determinant of the increments associated with the PASI response categories. There appear to be important differences across the studies, with the highest increments reported in the study with the lowest baseline EQ-5D. One potential explanation for the differences in the increments across the studies is that any ceiling effect of EQ-5D may be less evident in individuals with a lower baseline value.

In the absence of additional data for all three treatments, it is only possible to speculate on the reasons for differences both in terms of the baseline EQ-5D values and the increments associated with the PASI categories. However, since the PASI response rates from the NMA are assumed to be a perfect proxy for change in utility arising from treatment, it is difficult to argue that the higher increments reported for brodalumab are specific to the product and that the evidence for other treatments should not be considered further. It is also evident that the evidence for EQ-5D for brodalumab is also derived from a much smaller set of individuals (all patients; n=661) than for secukinumab (all patients; n=3,286) and ixekizumab (all patients; n=2,085).

Consequently, while the ERG considers that the EQ-5D data from AMAGINE-1 can be appropriately generalised to the other AMAGINE studies, uncertainties remain regarding their generalisability to

the broader studies included in the NMA. The ERG acknowledges, however, that the company sought to address these uncertainties using a series of scenario analyses, including using: (i) values from the all patient population from AMAGINE-1, (ii) estimates based on the 4th quartile of DLQI (TA103, TA155); (iii) estimates based on the secukinumab submission (TA350) for individuals with DLQI>10 and (iv) median values derived from the company SLR for previous STAs.

Despite these additional scenarios, the ERG considers that the markedly lower increments reported for ixekizumab have not been fully explored by the company in terms of their relevance and any possible implications for cost-effectiveness. The ERG further explores this specific issue as part of a series of additional exploratory analyses.

5.2.8 Resources and costs

The CS (section B.3.5 page 129) describes the search strategies used to identify studies of resource use and treatment costs. The database searches for resource use and costs (carried out alongside the search for economic evaluations) were carried out on 31st January 2017 and updated on 15th August 2017. The following databases were searched: MEDLINE, MEDLINE in Process, EMBASE, NHS Economic Evaluation Database (NHS EED), and EconLit. A number of conference proceedings were also searched for 2014 onwards, including: International Society for Pharmacoeconomics & Outcomes Research (ISPOR); International Congress on Psoriasis; World Congress of Dermatology; EADV; the American Academy of Dermatology and the British Association of Dermatologists Annual Meeting. The CEA Registry; the NICE HTA website; and the Scottish Medicines Consortium were also searched.

The ERG notes that the company searched for both published articles and grey literature using thorough searches of appropriate databases and conference proceedings. The structure of the search strategies was appropriate and the MEDLINE and Embase strategies incorporated a study design search filter to limit retrieval to economic studies & cost studies of brodalumab. The strategies contained relevant subject headings, text word searches and synonyms and all search lines were combined correctly. The search of the NHS EED correctly only used search terms for the topic (brodalumab and psoriasis) as the content of this resource is already pre-filtered to only include economic studies

The resource use and costs included in the model comprised drug acquisition, administration, monitoring, adverse events and BSC. Unit costs were sourced from relevant UK sources including: 2015/2016 reference costs; Monthly Index of Medical Specialties (MIMS); Personal Social Services Research Unit (PSSRU) and other published literature.

Drug acquisition costs

Drug costs were obtained from MIMS apart from for brodalumab, for which a PAS has been agreed, and ustekinumab 90 mg, which was attributed the same cost of ustekinumab 45 mg based on the non-confidential PAS. Assuming the NHS would give priority to biosimilars where available, the lower cost option of biosimilars for etanercept and infliximab was used in the base case. Etanercept was assumed to be administered as a 50mg per week dose. The cost of infliximab, which is weight-based, was calculated using a mean weight of 85.8 kg (sourced from the baseline characteristics of the trials included in the NMA). The induction period costs for apremilast and DMF include the specific titration periods for these drugs, before applying the usual daily dose during maintenance.

Table 22 summarises the drug acquisition costs applied in the company base case. The CS does not include the confidential PAS schemes which have been approved for apremilast, secukinumab and ixekizumab.

Table 22: Drug acquisition costs (adapted from CS Table 50 and Table 42)

Drug	Pack size	Dosage/ description	Cost per dose	Total cost (induction period)	Total cost (end of induction period to end of year 1)	Total annual cost (subsequent years)
Brodalumab (Kyntheum)	2	Injection of 210 mg on day 1 and weeks 1 and 2 and then every other week thereafter	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab (Humira)	2	Injection, initially 80 mg, then 40 mg on alternate weeks starting 1 week after initial dose	£352.14	£3,521.4	£6,338.52	£9,155.64
Apremilast (Titration pack)	690 mg	30 mg twice daily after an initial titration schedule	£19.64	£2,181.18	£4,954.91	£7,154.91
Apremilast	56					
Dimethyl fumarate (titration pack)	1,260 mg	The maximum dosage is 240 mg three times daily given orally, after an initial titration schedule	£12.72	£1,023.96	£3,208.62	£4,633.26
Dimethyl fumarate	90					
Etanercept 25 mg (Enbrel)	4	Injection, 25 mg twice weekly or 50 mg once weekly, for up to 24 weeks	£89.38	£2,145.00	£7,150.00	£9,295.00
Etanercept 50 mg (Enbrel)	4		£178.75	£2,145.00	£7,150.00	£9,295.00
Biosimilar etanercept 50 mg (Benepali)	4		£164.00	£1,968.00	£6,560.00	£8,528.00
Infliximab (Remicade)	1	By IV infusion, 5 mg/kg, repeated 2 weeks and 6 weeks	£2,098.10	£6,294.30	£10,490.50	£13,637.65
Infliximab	1		£1,855.00	£5,655.00	£9,425.00	£12,252.50

Drug	Pack size	Dosage/ description	Cost per dose	Total cost (induction period)	Total cost (end of induction period to end of year 1)	Total annual cost (subsequent years)
(Flixabi)		after initial infusion, then every 8 weeks				
Ixekizumab (Taltz)	1	Injection, initially 160 mg, then 80 mg every two weeks for 12 weeks. Maintenance: 80 mg every 4 weeks	£1,125.00	£7,875.00	£11,250.00	£14,625.00
Secukinumab (Cosentyx)	1	Injection of 300 mg at weeks 0, 1, 2 and 3 followed by monthly dosing from week 4. Each 300 mg injection is administered as two injections of 150 mg	£1,218.78	£7,312.68	£12,187.80	£14,625.36
Ustekinumab 45 mg (Stelara)	1	Injection, body weight < 100 kg, initially 45 mg, then 45 mg 4 weeks after initial dose, then 45 mg every 12 weeks. Bodyweight >100 kg, initially 90 mg, then 90 mg 4 weeks after initial dose, then 45 mg every 12 weeks	£2,147.00	£4,294.00	£6,441.00	£9,303.67
Ustekinumab 90 mg (Stelara)	1		£2,147.00	£4,294.00	£6,441.00	£9,303.67

An important determinant of the total costs for the different periods (induction, end of induction to end of year 1 and annually thereafter) is the different induction periods for each treatment and the different dosing regimens during and after induction. Table 23 provides a comparison of the dosing assumptions applied in the company base case.

Table 23: Comparison of induction periods and doses

Treatment	Induction period	Number of induction period doses	Total doses in year 1	Annual number of maintenance doses
Brodalumab	12 weeks	7	27	26
Adalimumab	16 weeks	10	28	26
Apremilast	16 weeks	109.5	361.75	364.25
Dimethyl fumerate	16 weeks	75.25	327.5	364.25
Etanercept	12 weeks	12	52	52
Infliximab	10 weeks	3	8	6.5
Ixekizumab	12 weeks	7	17	13
Secukinumab	12 weeks	6	16	12
Ustekinumab	16 weeks	2	5	4.33

Adapted from Table 42, company submission

The ERG considers that the assumptions regarding dosing for the comparator products appear consistent with previous NICE TAs. However, the ERG notes that there has been some variation reported between companies and ERGs in previous appraisals concerning the dosing assumptions applied during the induction period. Specifically, variation has emerged in the interpretation of the induction period itself. That is, whether the induction period refers to the duration of the initial treatment period or to the duration of the response assessment period. The specific source of variation has arisen in situations when a scheduled dose falls at the same time point of the response assessment period applied in the model. For example, the 7 doses assumed for ixekizumab are for a 10-week treatment period. In TA 442, the previous ERG argued that since the next scheduled dose was at the time point of the response assessment, that this dose (and ongoing treatment thereafter) would only be given to individuals who were responders at this time point. While this assumption might be debatable, the approach employed by the company in this submission is consistent with the approach taken in TA 442.

It should also be noted that the same issue regarding dosing applies to brodalumab. Here the argument for consistency with TA 442 is perhaps more compelling, since the assessment of response in the AMAGINE-trials at 12-weeks was taken after 10-weeks of treatment (i.e. 7 doses). However, from a costing perspective, there is also an important reason why the number of doses assumed by the company for brodalumab may require adjustment in the model. In contrast to other subcutaneous treatments, which can be prescribed in a variety of different pack sizes (including single syringes), the SPC for brodalumab states that this is currently only available in unit packs containing 2 pre-filled syringes (each providing a dose of 210mg) and in multipacks containing 6 (3 packs of 2) pre-filled syringes. Furthermore, the SPC does not appear to allow provision for unit packs to be split, since the

precautions note that the pre-filled syringe should be kept in the outer carton in order to protect from light.

From a costing perspective and adhering to the wording in the SPC, it appears reasonable to assume that all individuals will be prescribed 8 doses of brodalumab (i.e. 4 packs of 2 pre-filled syringes), even if individuals who are not responding at week 12 discontinue and do not take the final dose. The company base case analysis assumes that all patients receive 7 doses and that only patients who are responders will continue to receive the 27 doses during the 1st year of treatment (i.e. 20 additional doses in the period between induction and the end of the 1st year). From a costing perspective, the ERG considers it would be more consistent with the SPC to assume that all patients are prescribed 8 doses during the initial induction period and to adjust the additional doses in the period following this (i.e. 19 doses rather than 20) to avoid double counting this dose in responders. The implication of this proposed adjustment for cost-effectiveness is considered in the ERG exploratory analyses.

Administration costs

All subcutaneous treatments were assumed not to incur any administration costs. Initial training and assistance with administration was stated in the CS to be offered by the company via home care support. Similarly, no administration costs were assumed for oral therapies (apremilast and DMF). Infliximab was assumed to be administered as an intravenous (IV) injection performed by a health care professional and a cost of £96.48 was applied based on NHS Reference Costs.

The ERG notes that the assumption of no administration costs for subcutaneous treatments is not consistent with previous submissions. Both TA442 (ixekizumab) and TA350 (secukinumab) included nurse training cost for self-administration during the induction period. The most recent of these appraisals (TA 442) assumed that patients would undertake three 1-hour training sessions with a nurse, representing a total administration cost of £108. However, the ERG is also aware of ongoing appraisals where more detail has been provided regarding the provision and funding of homecare delivery services by companies which appear to include provision for home training.

The ERG concludes that while there is some uncertainty surrounding whether administration costs should be included for the subcutaneous treatments, their use seems unlikely to generate significant resource use and cost implications for the NHS. In addition, 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, with the exception of infliximab. The frequency of monitoring was based on the

recent BAD (2017) guideline (see Table 24 below). Unit costs were sourced from the 15/16 NHS Reference Costs.

Table 24: Frequency and total cost of treatment monitoring during trial and treatment periods for each drug (CS Table 52)

	Induction period		Maintenance period (per year)	
Drug	**Frequency**	**Total cost**	**Frequency**	**Total cost**
Brodalumab, adalimumab, apremilast, dimethyl fumarate, etanercept, ixekizumab, secukinumab and ustekinumab	2	£203.89	2	£203.89
Infliximab	3	305.83	2	£203.89

The ERG would like to highlight two specific issues concerning the frequency of treatment monitoring:

- Firstly, it should be noted that the annual frequency of monitoring during the maintenance period (2 visits) is lower than assumed in recent NICE TAs. For example, recent appraisals of ixekizumab (TA442) and DMF (TA475) have both assumed 4 annual visits during the maintenance period.[47, 62] Despite the inconsistency with previous NICE TAs, the ERG considers that the company is justified in making this change in light of the more recent BAD guideline.

- Secondly, the BAD guidelines did not consider DMF. The previous appraisal of DMF (TA475) included 2 additional monitoring visits, both in the initial induction period and during each annual maintenance period, compared to other biological and non-biological treatments due to safety concerns regarding progressive multifocal leukoencephalopathy (PML).[47]

The ERG concludes that it would appear appropriate to include an additional two outpatient visits (and corresponding blood tests) for DMF during the induction and annual maintenance periods, compared to the company assumptions. The impact of this is assessed in the ERG exploratory analyses.

Non-responder costs

The CS states that patients who fail to respond to biologics and switch to BSC may incur additional healthcare costs and that '*according to 2015/16 NHS Hospital Episode Statistics, patients with a diagnosis of psoriasis vulgaris who received inpatient care have an average length of stay of 10.3 days at a cost of £448.72 per day'*. However, the company also considered that incorporating these costs could result in over-estimation of inpatient care costs as these were already captured in the costs for patients receiving BSC. Consequently, the company excluded the costs of non-responders from

their base-case and instead presented a separate scenario based on assumption that non-responders would incur the full cost of an inpatient stay (10.3 days).

The ERG notes that the most recent 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 most recent STA for DMF included a cost of £128 per 2-week cycle.[47] Hence, the exclusion of these costs from the company base-case may be considered to be a conservative assumption for brodalumab compared to treatments with a lower PASI75 response. However, while an argument can be made for including the costs of non-responders, the assumption made by the company within their scenario appears extreme as it assumes that all non-responders will be hospitalised.

The ERG concludes that including a cost of £128 per 2-week cycle would be consistent with the source and assumptions previously applied in the most recent STA for DMF.[47]

BSC costs

The cost of BSC was based on Fonia et al. (2010),[63] an observational study reporting health care resource use and costs of 76 patients in the UK for a period of 1-year before starting biologic therapy. The company noted that this source has been used to inform the costs of BSC for the most recent NICE appraisals.

Table 25 presents a comparison of the baseline characteristics reported in Fonia et al (2010) and the AMAGINE trials.

Table 25: Comparison of baseline patients characteristics between Fonia and the AMAGINE trials

Study	% Male	Mean Age (years + SD)	Psoriasis Duration (years + SD)	PASI Score (SD)
Fonia	79%	47.3 (23-74)	24.7 (5.3-45.5)	18.7 (2.7-42.1)
AMAGINE–1	73%	47 ± 13	21 ± 12	19.7 ± 7.7
AMAGINE-2	71%	44 ± 13	18 ± 12	20.4 ± 8.2
AMAGINE–3	66%	44 ± 13	18 ± 12	20.1 ± 8.7

The following resource use and costs items were included: inpatient, intensive care unit and high dependency unit admissions; accident and emergency visits; outpatient visits; day ward admissions; and phototherapy. The costs were inflated to 2017 prices. An annual cost of £5,283 (2-weekly cycle cost equivalent=£203) was assumed.

The ERG requested additional information to validate the company estimates. These were provided by the company and the ERG considers that the estimates have been correctly estimated and appear consistent with the source and estimates used in previous NICE appraisals.

Adverse event costs

Cost of serious infection was included in the base case as its management has a large impact on costs. Cost of a serious infection was computed as the weighted average of six infection types: sepsis, tuberculosis, pneumonia, skin and soft tissue infection, bone and joint infection and urinary tract infection. Unit costs from NHS Reference Costs 15/16 are weighted for the number of finished consultant episodes reported in the same document, by relevant HRGs.

The costs applied in the company model are summarised in Table 26. The ERG considers the assumptions and estimates to be appropriate.

Table 26: Cost of treating adverse events (CS Table 55)

Adverse event	Adverse event sub-type	Unit cost	Mean cost	Source
Serious infection	Sepsis	£2,741.30	**£2,653.56**	NHS reference costs 2015/16: WJ06A-J
	Tuberculosis	£3,872.88		NHS reference costs 2015/16: DZ14F-J
	Pneumonia	£2,598.29		NHS reference costs 2015/16: DZ11K-V and DZ23H-N
	Soft tissue infection	£1,964.55		NHS reference costs 2015/16: HD21D-H
	Bone and joint infections	£4,777.47		NHS reference costs 2014/15: HD25-H
	Urinary tract infection	£2,615.81		NHS reference costs 2015/16: LA04H-S

5.2.9 Cost effectiveness results

Table 27 summarises the company base-case cost-effectiveness results based on their deterministic analysis. Fully incremental cost-effectiveness ratios (ICERs) and pairwise ICERs for the brodalumab sequence compared to each comparator sequence were reported.

Following conventional decision rules for cost-effectiveness, the mean costs and QALYs for the various sequences were presented and cost-effectiveness 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 DMF (sequence 9). The ICER of the brodalumab sequence (sequence 1) was reported to be £13,353 per QALY compared to the DMF sequence. 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 brodalumab sequence was £894,010 per QALY.

In the pairwise comparisons, the brodalumab sequence dominated the following sequences: adalimumab (sequence 2); infliximab (sequence 5); secuckinumab (sequence 7) and ustekinumab (sequence 8). The ICER of the brodalumab sequence compared to less effective and non-dominated sequences ranged from £7,145 (versus the etanercept sequence) to £13,353 (versus the DMF sequence). The ICER of the more effective ixekizumab sequence was £894,010 per QALY compared to the brodalumab sequence.

Table 27: Company base case deterministic results (adapted from CS Table 58)

Sequence	1st line	2nd line	3rd line	4th line	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY) fully incremental	ICER (£/QALY): BRO sequence vs comparator
9	DMF	UST	SEC	BSC	£146,101	12.64	£0	0	-	£13,353
3	APR	UST	SEC	BSC	£149,236	12.72	£3,136	0.07	Extendedly dominated	£9,955
4	ETN	UST	SEC	BSC	£151,791	12.82	£5,690	0.18	Extendedly dominated	£7,145
2	ADA	UST	SEC	BSC	£156,036	13.10	£9,935	0.46	Dominated	Dominated
8	UST	ADA	SEC	BSC	£156,156	13.10	£10,055	0.46	Dominated	Dominated
7	SEC	UST	ADA	BSC	£161,524	13.11	£15,423	0.47	Dominated	Dominated
5	INF	UST	SEC	BSC	£172,212	13.23	£26,111	0.59	Dominated	Dominated
1	BRO	UST	SEC	BSC	£155,517	13.35	£9,416	0.71	£13,353	N/A
6	IXE	UST	SEC	BSC	£182,957	13.38	£36,857	0.74	£894,010	£894,010

The company also presented ICER results from their probabilistic analysis. These were reported to be very similar to the deterministic estimates, indicating that model appears relatively linear. The company reported that at a threshold of £20,000 per QALY, the brodalumab sequence had the highest probability of being cost-effective (96%), followed by the DMF sequence (4%). At a £30,000 threshold, the brodalumab sequence was reported to have a 100% probability of being the most cost-effective of the sequences considered by the company.

5.2.10 Sensitivity analyses

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

The one-way DSA assessed the impact of single key variables on the final results. Across these analyses, the main driver of differences in the results was reported to be the acquisition costs (varied by +/-20 of the mean), the annual discontinuation rate and the cost of BSC.

The scenarios suggested the cost-effectiveness of brodalumab was most sensitive to assumptions related to discontinuation rates, utility values and BSC efficacy.

5.2.11 Model validation and face validity check

The company reported that several validation steps had been performed, including:

(i) an advisory board made up of both clinical and health economic experts was consulted to support model development;

(ii) the model developers and another health economist who had not been involved in the model's development conducted quality control and checked for internal and external validity.

(iii) extreme value analysis, cell-by-cell technical validation of the model was carried out and visual basic code checked.

The ERG conducted its own validation of the visual basic code, the Excel functions and linkages between spreadsheets (cell-by-cell validation) that produced the modelling outputs. All the VBA code and linkages were correctly functioning and model inputs were found to match those reported of the submission with one minor exception that had no noticeable impact on the final results. The pack cost of apremilast used in the latest submitted version of the model is £256.18 whilst, as acknowledged by the company in their response to clarification points raised by the ERG, the correct cost is £265.18.

The company base case and sensitivity analysis scenarios were successfully reproduced by the ERG in deterministic and probabilistic analyses. Basic logical tests performed by the ERG entering extreme values for costs and efficacy and 0-1 values for utility showed the model behaved logically.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG review identified 5 key areas of uncertainty in the CS relating to the following main issues:

1. Sequences
2. NMA, placebo adjustment and heterogeneity in trial baselines
3. HRQoL
4. Costs
5. Withdrawal

Each of these issues is explored separately by the ERG in the following section and the cost-effectiveness results reported. Importantly, all of the analyses presented by the ERG in this section are based on deterministic results. Although the company model is capable of performing probabilistic analyses, each run of the model takes approximately 2-3 hours. Given the similarity between the deterministic and probabilistic results reported by the company, the ERG does not consider this an important limitation for the purposes of these exploratory analyses.

In Section 6, the ERG proposes an alternative ERG base-case which draws on these exploratory analyses. The results reported in the ERG alternative base-case are based on probabilistic analyses.

Full results of all the individual analyses are provided in Appendix 10.3. The equivalent tables including the confidential PAS schemes for apremilast, ixekizumab and secukinumab are also provided in a separate confidential appendix to the ERG report.

Issue 1: Sequencing

In Section 5.2.4, the ERG concluded that the sequences evaluated by the company were restrictive in terms of the number of sequences included and the position of brodalumab with these. The ERG also noted the concerns 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, particularly if there are treatments included in a sequence which are not cost-effective themselves.

The ERG proposes an alternative approach to informing the cost-effectiveness of brodalumab which more fully addresses these issues and concerns. Specifically, the ERG approach proposes the use of the net benefit framework[64] as opposed to the conventional decision rules for CEA which are based on the ICER.

A limitation of conventional decision rules is that the interpretation of negative and positive ICERs is ambiguous without reference to the cost-effectiveness plane. That is, the intervention of interest is

regarded as cost-effective if its incremental cost-effectiveness ratio is lower than the threshold (($\Delta C/\Delta E < \lambda$; where λ is between £20,000 - £30,000 per QALY) for ICERs in the NE quadrant of the cost-effectiveness plane (i.e. the intervention is more costly and more effective than the comparator) or higher than the threshold ($\Delta C/\Delta E > \lambda$) for ICERs in the SW quadrant (i.e. the intervention is less costly and less effective).

Net-benefits can be expressed on the effect scale (incremental net health benefits) or the cost scale (incremental net monetary benefits) and are estimated by re-arranging the elements of the conventional ICER equation, where:

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

Incremental net health benefits (NHB) = $\Delta E - \Delta C/\lambda$

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, then the intervention is considered to be cost-effective. A further advantage of using the net-benefit framework in the current appraisal is that it is also possible to simplify the fully incremental comparisons and also the sequential treatment comparisons, due to 2 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 proposes that the incremental net-benefits of each individual treatment versus BSC alone (and associated rankings) can also 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);

The ERG's approach is illustrated in Table 28 (ERG Exploratory Analysis 1). This table presents a comparison of each individual treatment compared to BSC alone using the company base-case assumptions. Estimates of the incremental cost and QALY and the pairwise ICER of each treatment

versus BSC alone are presented. In addition, the incremental NMB of each individual treatment versus BSC at a £20,000 and £30,000 per QALY threshold are also reported.

The relationship between the NMB and the ICER estimate are evident. 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).

The results from Table 28 indicate that the following treatments would not appear in any efficient sequence using either a £20,000 or £30,000 per QALY threshold: infliximab, secukinumab and ixekizumab. The ERG notes that these results do not include the confidential PAS schemes for secukinumab and ixekizumab (reported separately in the ERG's confidential appendix). All of the remaining treatments have the potential to be in an efficient sequence depending on whether there are constraints on the overall length of a sequence.

Table 28: ERG Exploratory Analysis 1 (company base-case assumptions) - Incremental net-benefit and rankings

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	Pairwise ICER vs BSC	INB vs BSC @20k	Rank @20k	INB vs BSC @30k	Rank @30k
BSC	10.67	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.81	£113,873	1.14	£14,236	£12,540	£8,468	**1**	£19,821	**1**
Dimethyl fumarate	10.90	£98,899	0.23	-£737	Dominant	£5,238	**2**	£7,489	4
Adalimumab	11.50	£112,695	0.83	£13,058	£15,816	£3,454	**3**	£11,710	**3**
Apremilast	10.99	£102,705	0.32	£3,069	£9,479	£3,406	4	£6,643	6
Ustekinumab	11.57	£114,617	0.90	£14,981	£16,714	£2,945	5	£11,908	**2**
Etanercept 50 mg per week	11.13	£106,087	0.46	£6,451	£13,903	£2,829	6	£7,469	5
Infliximab	11.66	£129,759	0.99	£30,122	£30,460	-£10,344	7	-£455	7
Secukinumab	11.74	£139,036	1.07	£39,400	£36,969	-£18,085	8	-£7,427	9
Ixekizumab	11.84	£141,502	1.17	£41,865	£35,695	-£18,408	9	-£6,679	8

INB = Incremental net monetary benefit; ICER = incremental cost-effectiveness ratio, BSC = Best supportive care

The company submission 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 threshold, the optimal ranking based on NMB (vs BSC alone) is: brodalumab, DMF, adalimumab.

- At a £30,000 threshold, the optimal ranking based on NMB changes to: brodalumab, ustekinumab and adalimumab.

The ERG notes that with the 2 key assumptions made by the company, the only advantage of formally modelling sequences, as opposed to generalising from the single drug comparisons, is that the impact of mortality (i.e. the individual's age at the start of the 1st treatment and subsequent treatments will differ and not all patients will ultimately receive all lines of therapy due to the competing risk of mortality) and discounting are more appropriately captured using a sequence approach.

The impact of mortality and discounting are shown more clearly in Table 29. This table compares the NMB of all the alternative possible sequences of the 3 individual treatments with the highest NMB rankings versus BSC. At a £20,000 per QALY threshold, the optimal ranking based on NMB of each individual therapy versus BSC is: brodalumab, DMF, adalimumab. However, when the alternative treatment sequences themselves are compared (i.e. rather than single lines of treatment), the most efficient sequence (i.e. the sequence with the highest NMB) implies a different ordering: DMF, brodalumab, adalimumab.

In the absence of discounting and mortality, the NMB of the different sequences compared in Table 29 would be identical. The reason for differences is due to the impact of discounting and mortality. That is, not all individuals will ultimately survive to receive all 3 lines of treatments. Accordingly, from a pure efficiency perspective, it would makes sense to start to start with the treatment with the highest 'bang for buck' (i.e. the lowest ICER vs BSC), rather than starting with the treatment with the highest NMB (vs BSC). However, from a health maximisation perspective, a different ordering would also emerge (i.e. brodalumab, adalimumab, DMF). The ERG notes that the precise ordering of treatments within an overall sequence depends on the mortality and discount rate and the impact of these on the optimal ordering of treatments within a sequence ultimately depends on the overall objective function (e.g. pure efficiency vs health maximisation vs patient preference).

Table 29: Efficiency ranking of treatments within a sequence based only on cost-effectiveness considerations

First drug in sequence	Second drug in sequence	Third drug in sequence	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB @20k	Rank @20k
BSC	BSC	BSC	10.670	£99,637	NA	NA	NA	NA	NA
Dimethyl Fumarate	Adalimumab	Brodalumab	12.640	£123,373	1.970	£23,736	£12,050	£15,659	3
Adalimumab	Dimethyl Fumarate	Brodalumab	12.649	£124,020	1.979	£24,384	£12,324	£15,188	5
Dimethyl Fumarate	Brodalumab	Adalimumab	12.649	£123,091	1.979	£23,454	£11,852	£16,123	**1**
Adalimumab	Brodalumab	Dimethyl Fumarate	12.662	£124,686	1.992	£25,049	£12,575	£14,791	6
Brodalumab	Dimethyl Fumarate	Adalimumab	12.664	£123,814	1.993	£24,178	£12,128	£15,692	2
Brodalumab	Adalimumab	Dimethyl Fumarate	12.672	£124,395	2.001	£24,758	£12,371	£15,269	4

Despite the limitations of the single line comparisons, the ERG considers that these comparisons provide important contextual information. Using these comparisons it is possible to determine which treatments would form part of an optimal sequence of a particular length (e.g. the most efficient sequence with 3 active lines will always contain the 3 treatments with the highest NMB vs BSC). However, the precise ordering of treatments would then need to related to more clearly to the decision maker's objective function and the relative importance placed on maximising efficiency vs other objectives (e.g. maximisation of health, patient preferences etc).

More importantly the ERG considers that the net-benefit approach more fully addresses concerns noted by previous ERGs and NICE committees regarding the possible implications of restricting sequences (as opposed to modelling all feasible sequences) and the potential for misleading estimates of cost-effectiveness for the treatment of interest (i.e. due to the inclusion of other treatments in a sequence which are not cost-effective themselves).

The ERG notes that the 2 key assumptions which underpin the base-case analysis (and the ERG's proposed approach based on a net-benefit framework) were explored by the company using an effect modifier from a Danish registry study. An odds ratio of 1.24 was subsequently used by the company to explore the following 3 scenarios:

A) to adjust the probabilities of primary response during induction (by dividing each level of PASI response by 1.24) – *representing possible effect modification related to primary failure*;

B) to adjust the annual discontinuation rate, increasing the rate of drop-outs for people with prior exposure – *representing possible effect modification related to secondary failure*; and

C) A and B combined - *representing possible effect modification related to both primary and secondary failures.*

A potential limitation of the ERG's proposed approach is that differential effects between 1st and subsequent lines cannot be incorporated when comparing only single lines of treatment. However, since the adjustments (i.e. odds ratio of 1.24) are not applied differentially across the separate treatments (i.e. suggesting that the effect modification may relate to one treatment but not another), the possible implications of effect modification can still be explored. That is, the NB for the single line of treatments (versus BSC alone) can simply be re-estimated with the adjustment applied, to establish whether: (a) treatments which appeared to be potentially cost-effective within a sequence without effect modification still appear to be cost-effective and (b) the rankings of treatment are affected or not.

Table 30 (ERG Exploratory Analysis 2) replicates the previous ERG exploratory analysis but applies an effect modification to the primary failure rates (i.e. akin to Scenario A presented by the company). The results indicate that those treatments which reported a positive NMB versus BSC alone without effect modification still show positive NMBs with effect modification. However, the rankings of NMB differ.

ERG Exploratory Analysis 2 (effect modification) rankings:

At a £20,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is: *brodalumab, DMF, apremilast*
- Treatments not in any efficient sequence are: *infliximab, secukinumab and ixekizumab*

At a £30,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) changes to: *brodalumab, ustekinumab, adalimumab*
- Treatments not in any efficient sequence are: *infliximab, secukinuma and ixekizumab*

The only change in this exploratory analysis, compared to the previous analysis without any effect modification, is that apremilast is now ranked 3rd at a £20,000 threshold. However, the optimal ranking at a £30,000 threshold is unchanged by the inclusion of effect modification.

Table 30: ERG Exploratory Analysis 2 (effect modification) - Incremental net-benefit and rankings

Drug (1 line only)	Total QALYs	costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	10.67	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.58	£111,373	0.91	£11,736	£12,840	£6,545	**1**	£15,685	1
Dimethyl fumarate	10.85	£98,966	0.18	-£671	Dominant	£4,262	**2**	£6,057	4
Apremilast	10.93	£102,260	0.26	£2,623	£10,123	£2,559	**3**	£5,151	6
Adalimumab	11.33	£110,573	0.66	£10,937	£16,475	£2,340	4	£8,979	**3**
Etanercept 50 mg per week	11.04	£105,023	0.37	£5,387	£14,452	£2,068	6	£5,795	5
Ustekinumab	11.39	£112,271	0.72	£12,634	£17,526	£1,783	5	£8,992	**2**
Infliximab	11.47	£124,940	0.80	£25,304	£31,777	-£9,378	7	-£1,415	7
Secukinumab	11.53	£132,625	0.86	£32,988	£38,447	-£15,828	8	-£7,247	9
Ixekizumab	11.61	£134,722	0.94	£35,085	£37,150	-£16,197	9	-£6,753	8

The ERG notes that there exists significant uncertainty surrounding the existence and possible magnitude of any effect modification. Although evidence from the Danish registry study suggests that switching from one drug agent to another is associated with impaired drug survival, it is also possible that these effects are due to potential selection effects (i.e. the more difficult to treat individuals are more likely to switch earlier). However, since the model predicts over much longer periods of time, inevitably all individuals will switch treatments multiple times over the model time horizon and hence estimates for the average patient experience are required (i.e. as opposed to the experience of early switchers). It is unclear whether the odds ratio in this context can be generalised to the average patient experience. Furthermore, subgroup analysis according to prior biologic therapy did not suggest that the absolute PASI responses for brodalumab were significantly different across subgroups, although baseline PASI responses for placebo did appear to vary.

Issue 2: NMA, placebo adjustment and heterogeneity in baseline

In Section 4.4.1, the ERG proposed minor revisions to the WinBUGs code and stated a clear preference for the placebo-adjustment model. The ERG also concluded that, in recognising the existing baseline risk heterogeneity of PASI response across included trials, the heterogeneity in baseline risk across the three pivotal phase 3 RCTs for brodalumab (i.e. the AMAGINE trials) should also be considered more explicitly.

A series of additional exploratory analyses were undertaken using the ERG revised coding based on the placebo-adjustment models and using alternative placebo PASI 50 response outcomes. These included:

- ERG Exploratory Analysis 3: ERG revisions to Winbugs code with placebo-adjustment (baseline placebo response derived from all trials in NMA)
- ERG Exploratory Analysis 4: ERG revisions to Winbugs code with placebo-adjustment (baseline placebo response derived from AMAGINE-1 only)
- ERG Exploratory Analysis 5: ERG revisions to Winbugs code with placebo-adjustment (baseline placebo response derived from AMAGINE-2/3 only)

Full tables of results are provided in a separate appendix. In summary, the same treatments and rankings were consistently identified across all three analyses.

At a £20,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is: *brodalumab, DMF, apremilast*

At a £30,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is: *brodalumab, adalimumab, ustekinumab*

The ERG notes that the main change evident in these scenarios was the inclusion of apremilast as the 3rd highest ranked treatment at a £20,000 threshold and a reversal of the ordering of adalimumab and ustekinumab at a £30,000 threshold.

Issue 3: HRQoL

In Section 5.2.7, the ERG reported that the regression model adjusting for baseline EQ-5D to be the most appropriate approach presented by the company. The results from the alternative regression approaches showed that the model including baseline EQ-5D only consistently performed better in terms of goodness of fit across a range of measures (e.g. AIC, BIC etc).

The ERG undertook 2 additional exploratory analyses using their preferred regression approach and estimates based on the DLQI>10 subgroup (company base-case) and the ITT population.

- ERG Exploratory Analysis 6: Utility regression adjusting for baseline EQ-5D (DLQI>10 subgroup)
- ERG Exploratory Analysis 7: Utility regression adjusting for baseline EQ-5D (ITT population)

ERG Exploratory Analysis 6 (Utility regression adjusting for baseline EQ-5D: DLQI>10 subgroup) ranking results:

At a £20,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is: *brodalumab, DMF, adalimumab*
- Treatments not in any efficient sequence are: *infliximab, secukinumab and ixekizumab*

At a £30,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is: *brodalumab, ustekinumab, adalimumab*
- Treatments not in any efficient sequence are: *infliximab, secukinumab and ixekizumab*

No changes were evident in this analysis compared to the ERG's 1st analysis employing the company base-case assumptions.

ERG Exploratory Analysis 7 (Utility regression adjusting for baseline EQ-5D: ITT population) ranking results**:**

At a £20,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is*: brodalumab, DMF, apremilast*
- Treatments not in any efficient sequence are: *infliximab, secukinumab and ixekizumab*

At a £30,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is: *brodalumab, adalimumab, ustekinumab*
- Treatments not in any efficient sequence are: *infliximab, Secukinumab, Ixekizumab*

The only change in this exploratory analysis, compared to the ERG's 1st analysis, is that apremilast now appears as the 3rd highest ranked treatment at a £20,000 threshold and the reversal of the ordering of adalimumab and ustekinumab at a £30,000 threshold.

In Section 5.2.7 the ERG noted that that the markedly lower increments reported for ixekizumab were not explained or explored further by the company in terms of their relevance and any possible implications for cost-effectiveness. The ERG further explored the EQ-5D-3L crosswalk values reported for ixekizumab by Pickard et al (2017), using these estimates for the baseline and PASI increments in the model.

ERG Exploratory Analysis 8: External utility estimates: EQ-5D-3L crosswalk values reported for ixekizumab - ranking results**:**

At a £20,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is*: DMF*
- Treatments not in any efficient sequence are: *brodalumab, apremilast etanercept adalimumab, infliximab, ixekizumab, secukinumab and ustekinumab*

At a £30,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is: *DMF, apremilast, brodalumab*
- Treatments not in any efficient sequence are: *adalimumab, infliximab, ixekizumab, secukinumab and ustekinumab*

The use of external utility estimates clearly has an important effect on the results. At a £20,000 threshold, brodalumab did not appear in any efficient sequence. At a £30,000 threshold, brodalumab was ranked third.

Issue 4: Costs

In Section 5.2.8, the ERG identified 3 specific issues with resource use and cost assumptions made in the company base-case.

Firstly, the ERG concluded that an adjustment to the dosing assumptions for brodalumab was appropriate based on the current SPC wording and the provision of 2-injections within each prescription pack. The ERG proposed that the dosing assumptions during the induction period for brodalumab should be increased to 8 (versus 7 assumed in the CS) and the doses in the period from induction to the end of year 1 reduced to 19 (versus 20 assumed in the CS). The impact of this is considered in the following exploratory scenario:

ERG Exploratory Analysis 9: Adjustment to brodalumab dosing assumptions - ranking results:

At a £20,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is*: brodalumab, DMF, adalimumab*
- Treatments not in any efficient sequence are: *infliximab, secukinumab and ixekizumab*

At a £30,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is: *brodalumab, ustekinumab, adalimumab*
- Treatments not in any efficient sequence are: *infliximab, secukinumab, ixekizumab*

The ERG notes that the rankings were unaffected by this change.

Secondly, the ERG concluded that considers that including a cost of £128 per 2-week cycle for non-responders would be consistent with the source and assumptions applied in recent appraisals. The following scenario considers the impact of including these non-responder costs

ERG Exploratory Analysis 10: Inclusion of non-responder costs - ranking results:

At a £20,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is*: brodalumab, DMF, adalimumab*

- Treatments not in any efficient sequence are: *infliximab, secukinumab and ixekizumab*

At a £30,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is: *brodalumab, ustekinumab, adalimumab*
- Treatments not in any efficient sequence are: *infliximab, secukinumab, ixekizumab*

The ERG notes that the rankings were unaffected by this change.

Finally the ERG concluded that additional monitoring for DMF should be included because of concerns regarding PML. In this scenario the ERG increased number of monitoring visits for DMF to 4 for both the induction and annual maintenance periods in line with the previous NICE appraisal.[47]

ERG Exploratory Analysis 11: Inclusion of additional monitoring costs for DMF - ranking results:

At a £20,000 per QALY threshold:

- The most efficient sequence is*: brodalumab, DMF, adalimumab*
- Treatments not in any efficient sequence are: *infliximab, secukinumab and ixekizumab*

At a £30,000 per QALY threshold:

- The most efficient sequence is: *brodalumab, ustekinumab, adalimumab*
- Treatments not in any efficient sequence are: *infliximab, secukinumab, ixekizumab*

The ERG notes that the rankings were unaffected by this change.

Issue 5: Withdrawal

In Section 5.2.6, the ERG noted that the company had assumed a constant annual discontinuation rate of 18.7% was applied in the maintenance period to all treatments (except BSC). The company also presented a separate scenario where the discontinuation rate was differentiated by treatment class. In this scenario the lower withdrawal rates reported for ustekinumab in BADBIR (compared to anti-TNF treatments) were generalised to a class effect applying to all the IL-inhibitors (i.e. brodalumab, ixekizumab, secukinumab and ustekinumab).

In the absence of similar data reported for the IL-17 treatments (brodalumab, ixekizumab and secukinumab), an additional exploratory analysis was undertaken by the ERG using a differential withdrawal rate for ustekinumab only (7.3% vs 18.5% assumed for all other comparators).

ERG Exploratory Analysis 12: Lower withdrawal for ustekinumab only - ranking results:

At a £20,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is*: brodalumab, ustekinumab, DMF*
- Treatments not in any efficient sequence are: *infliximab, secukinumab and ixekizumab*

At a £30,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is: *ustekinumab, brodalumab, adalimumab*
- Treatments not in any efficient sequence are: *infliximab, secukinumab, ixekizumab*

The use of a differential withdrawal rate for ustekinumab clearly has an important effect on the results. Ustekinumab was ranked 2nd and 1st at a £20,000 and £30,000 threshold, respectively.

Although the ERG considers that the assumptions applied in the base case analysis more justifiable than those considered by the scenario, the ERG also recognises that there exists significant uncertainty concerns both the rate itself and whether there are important treatment or class specific differences. However, the scenario clearly highlights the potential importance of longer term durability of effect for cost-effectiveness.

5.4 Conclusions of the cost effectiveness section

The ERG considered the company's economic submission to meet the requirements of the NICE reference case and to be of high-quality generally. However, the ERG identified a number of key uncertainties which warranted additional exploratory analyses. The ERG also 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 key uncertainties were assessed in 12 separate scenarios by the ERG. The scenarios and justification are summarised in Table 31. The impact of these on the efficiency rankings is summarised in Table 32 and Table 33.

Table 31: Summary of ERG exploratory scenarios

ERG Scenario Number	Description	ERG revised approach/assumptions	Justification
1	Company base-case assumption.	Net-benefit rankings of single treatment lines versus BSC.	More fully addresses concerns noted by previous ERGs and NICE committees regarding the possible implications of restricting sequences and the potential for misleading estimates of cost-effectiveness for the treatment of interest.
2	Effect modification.	Adjusted primary response data using odds ratio of 1.24.	To account for possible effect modification in later lines due to increased primary failure.
3	ERG revisions to Winbugs code with placebo-adjustment (baseline placebo response derived from all trials in NMA).	ERG revised coding implemented using placebo-adjusted synthesis model – baseline from all trials in NMA.	ERG revisions allowed the use of true uninformative priors. The ERG considers the placebo adjusted synthesis model to be more appropriate than the unadjusted model.
4	ERG revisions to Winbugs code with placebo-adjustment (baseline placebo response derived from AMAGINE-1 only).	ERG revised coding implemented using placebo-adjusted synthesis model – baseline from AMAGINE-1.	As 3. To further explore the impact of heterogeneity in the placebo response data.
5	ERG revisions to Winbugs code with placebo-adjustment (baseline placebo response derived from AMAGINE-2/3 only).	ERG revised coding implemented using placebo-adjusted synthesis model – baseline from AMAGINE 2/3.	As 3. To further explore the impact of heterogeneity in the placebo response data.
6	Utility regression adjusting for baseline EQ-5D: DLQI>10 subgroup.	Regression estimates derived from company response (Model B3a) – DLQI>10 subgroup.	ERG preferred regression with best performance in terms of statistical goodness of fit.
7	Utility regression adjusting for baseline EQ-5D: All patients.	Regression estimates derived from company response (Model B3a) – all patients.	As 6. To explore uncertainties regarding the use of subgroup versus all patient values.

8	External utility estimates: EQ-5D-3L crosswalk values reported for ixekizumab.	Estimates from AMAGINE-1 (DLQI>10) replaced with values reported by Pickard et al (2017).	To explore the impact of variation identified in the EQ-5D estimates. Specific focus on the impact of assuming a higher baseline utility and lower decrements compared to those reported in AMAGINE-1.
9	Adjustment to brodalumab dosing assumptions.	Altered estimates for brodalumab during the induction period (8 versus 7 doses) and for the post-induction to end of year 1 period (19 versus 20 doses).	Based on ERG's interpretation of the SPC. Brodalumab is currently only available in unit packs containing 2 pre-filled syringes (each providing a dose of 210mg) and in multipacks containing 6 (3 packs of 2) pre-filled syringes. The SPC does not appear to allow provision for unit packs to be split.
10	Inclusion of non-responder costs.	£128 applied per 2-week cycle during the induction period for non-responders.	Consistent with recent NICE appraisals.
11	Inclusion of additional monitoring costs for DMF.	2 additional monitoring visits assumed for DMF during the induction period and annually during the maintenance phase.	Concerns regarding progressive multifocal leukoencephalopathy (PML). Consistency with NICE TA 475.
12	Lower withdrawal for ustekinumab only	Discontinuation rate of 7.3% assumed for ustekinumab (vs 18.7% for other treatments)	Based on lower withdrawal reported for ustekinumab vs other anti-TNFs in BADBIR. Lack of evidence for class-effect related to all IL-inhibitors.

Table 32: ***Summary of ERG exploratory scenarios and rankings (£20,000 threshold)***

Treatment	ERG Exploratory Scenarios											
	1	2	3	4	5	6	7	8	9	10	11	12
	Rankings											
Brodalumab	1	1	1	1	1	1	1	4	1	1	1	1
Adalimumab	3	4	4	3	4	3	5	5	3	3	3	4
Apremilast	4	3	3	4	3	5	3	2	6	4	4	5
DMF	2	2	2	2	2	2	2	1	2	2	2	3
Etanercept	6	6	6	6	5	6	4	3	6	6	6	6
Infliximab	7	7	7	7	7	7	7	7	7	7	7	7
Ixekizumab	9	9	9	9	9	9	9	9	9	9	9	9
Secukinumab	8	8	8	8	8	8	8	8	8	8	8	8
Ustekinumab	5	5	5	5	6	4	6	6	5	5	5	2

Table 33: ***Summary of ERG exploratory scenarios and rankings (£30,000 threshold)***

Treatment	ERG Exploratory Scenarios											
	1	2	3	4	5	6	7	8	9	10	11	12
	Rankings											
Brodalumab	1	1	1	1	1	1	1	3	1	1	1	2
Adalimumab	3	3	2	2	2	3	2	5	3	3	3	3
Apremilast	6	6	5	5	5	6	6	2	6	6	5	6
DMF	4	4	4	4	3	5	4	1	4	5	6	4
Etanercept	5	5	6	6	6	4	5	4	5	4	4	5
Infliximab	7	7	7	7	7	7	7	7	7	7	7	7
Ixekizumab	8	8	8	8	8	8	8	9	8	8	8	8
Secukinumab	9	9	9	9	9	9	9	8	9	9	9	9
Ustekinumab	2	2	3	3	4	2	3	6	2	2	2	1

At a £20,000 threshold, brodalumab was ranked 1st in 11 of the 12 scenarios. The only scenario where brodalumab was ranked lower than 1st (and indeed didn't form part of the most efficient 3-line treatment sequence) was when the cross-walked EQ-5D-3L values reported for ixekizumab were used instead of the estimates derived from AMAGINE-1 (ERG Scenario 8).

At a £30,000 threshold, brodalumab was ranked 1st in 10 of the 12 scenarios explored by the ERG. The only scenario where brodalumab was ranked lower than 1st was: (i) when the cross-walked EQ-5D-3L values reported for ixekizumab were used instead of the estimates derived from AMAGINE-1

(ERG Scenario 8) and (ii) when a lower withdrawal rate was assumed for ustekinumab (ERG Scenario 12).

Although Scenario 8 clearly demonstrates that the utility values applied in the model are a key driver of the cost-effectiveness results, there ERG is not aware of any systematic reason for the marked differences between the utility values aside from one being based directly on EQ-5D-3L values and the other based on cross-walked EQ-5D-3L values). While this raises interesting issues regarding the respective properties of EQ-5D-3L and EQ-5D-5L, the ERG considers that the values used in the company base-case more closely meet the requirements of the current NICE reference case and hence are most relevant values to be considered.

Similarly, while Scenario 12 (differential withdrawal rate for ustekinumab only), clearly highlights the potential importance of longer term durability of effect for cost-effectiveness, the ERG considers that the assumptions applied in the company base case analysis (i.e. common withdrawal for all treatments) appear more justifiable than those considered by the scenario. However, the ERG recognises that there exists significant uncertainty concerns both the rate itself and whether there are important treatment or class specific differences and that there exists more limited longer-term data to assess the durability of treatment response for brodalumab compared to ustekinumab and the anti-TNFs.

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

In Section 5, the ERG presented a series of 12 exploratory analyses to further consider uncertainties related to several key aspects and assumptions in the company base-case. Each of these analyses explored the impact of individual changes applied to the company model. Although the ERG considers that the range of scenarios are helpful in highlighting the key cost-effectiveness drivers (i.e. particularly utilities and withdrawal rates), the ERG did not consider that all of these represented more plausible assumptions or scenarios than those included in the company base-case.

Table 34 summarises the specific scenarios which the ERG consider represent more appropriate or plausible assumptions. The scenarios are combined within the ERG alternative base-case. The combined impact of these is reported in Table 35.

Table 34: Summary of ERG exploratory scenarios included in alternative ERG base-case

ERG Scenario Number	Description	ERG revised approach/assumptions	Justification
1	Company base-case assumption.	Net-benefit rankings of single treatment lines versus BSC.	More fully addresses concerns noted by previous ERGs and NICE committees regarding the possible implications of restricting sequences and the potential for misleading estimates of cost-effectiveness for the treatment of interest.
3	ERG revisions to Winbugs code with placebo-adjustment (baseline placebo response derived from all trials in NMA).	ERG revised coding implemented using placebo-adjusted synthesis model – baseline from all trials in NMA.	ERG revisions allowed the use of true uninformative priors. The ERG considers the placebo adjusted synthesis model to be more appropriate than the unadjusted model.
6	Utility regression adjusting for baseline EQ-5D: DLQI>10 subgroup.	Regression estimates derived from company response (Model B3a) – DLQI>10 subgroup.	ERG preferred regression with best performance in terms of statistical goodness of fit.
9	Adjustment to brodalumab dosing assumptions.	Altered estimates for brodalumab during the induction period (8 versus 7 doses) and for the post-induction to end of year 1	Based on ERG's interpretation of the SPC. Brodalumab is currently only available in unit packs containing 2 pre-filled syringes (each providing a dose of 210mg) and in multipacks containing

		period (19 versus 20 doses).	6 (3 packs of 2) pre-filled syringes. The SPC does not appear to allow provision for unit packs to be split.
10	Inclusion of non-responder costs.	£128 applied per 2-week cycle during the induction period for non-responders.	Consistent with recent NICE appraisals.
11	Inclusion of additional monitoring costs for DMF.	2 additional monitoring visits assumed for DMF during the induction period and annually during the maintenance phase.	Concerns regarding progressive multifocal leukoencephalopathy (PML). Consistency with NICE TA 475.

Table 35: ERG alternative base-case: probabilistic results

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	10.59	£100,869	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.81	£114,958	1.2	£14,089	£11,549	£10,308	**1**	£22,507	**1**
Dimethyl fumarate	11.00	£100,919	0.4	£49	£120	£8,146	**2**	£12,243	4
Adalimumab	11.55	£114,468	1.0	£13,599	£14,183	£5,578	**3**	£15,166	**2**
Apremilast	11.02	£104,802	0.4	£3,933	£9,203	£4,614	4	£8,887	6
Ustekinumab	11.57	£115,822	1.0	£14,952	£15,331	£4,553	5	£14,306	**3**
Etanercept 50 mg per week	11.11	£107,562	0.5	£6,692	£12,837	£3,734	6	£8,948	5
Infliximab	11.66	£130,734	1.1	£29,865	£27,915	-£8,468	7	£2,231	7
Secukinumab	11.71	£139,440	1.1	£38,570	£34,414	-£16,155	8	-£4,947	9
Ixekizumab	11.82	£142,027	1.2	£41,157	£33,463	-£16,558	9	-£4,259	8

ERG Alternative Base-Case rankings:

At a £20,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is: brodalumab, DMF, adalimumab
- Treatments not in any efficient sequence are: infliximab, secukinumab and ixekizumab

At a £30,000 per QALY threshold:

- The optimal ranking based on NMB (vs BSC alone) is: brodalumab, adalimumab, ustekinumab
- Treatments not in any efficient sequence are: secukinumab and ixekizumab

The ERG notes that the optimal ranking identified in their alternative base-case are identical to those derived from the company base-case model. The only difference identified is that infliximab has a positive NMB at a £30,000 threshold in the ERG alternative-base case, indicating that this treatment could form part of an efficient sequence of longer length (i.e. when more than 3 active lines of therapies are evaluated).

The ERG concludes that their alternative assumptions have no material effect on the conclusions that can be drawn from the company base-case. Importantly, brodalumab was identified as the most efficient treatment (i.e. the highest rank based on NMB vs BSC alone) in the ERG and company base-case analyses. The ERG considers that this provides significant reassurance and confirmation regarding the robustness of the company's results.

7 End of life

This intervention does not meet the end of life criteria published by NICE.

8 Overall conclusions

The trials demonstrated that brodalumab 210mg Q2W significantly reduced the severity of psoriasis compared with placebo and ustekinumab and subgroup analyses demonstrate these effects regardless of disease severity or prior exposure to systemic therapy, phototherapy and biological therapy. All three of the AMAGINE trials were good quality RCTs and the results are likely to be reliable. However, the results of the AMAGINE trials may not be entirely generalisable to the proposed eligible population because inclusion criteria relating to disease severity were not the same as the threshold specified in the NICE treatment pathway, 17-35% patients in the AMAGINE trials had not received previous systemic therapy or phototherapy and the AMAGINE trials excluded patients who had previously received ustekinumab or anti-IL-17 therapy.

The ERG considers that the NMA was conducted appropriately to compare treatments. However, there was considerable variation in PASI response rates in the placebo arms of the trials included in the NMA. Results from a placebo adjusted synthesis model were similar to those from the unadjusted model: the treatment rankings were unaltered. When ranked in order of effectiveness (median probability of achieving a PASI 75 response), the results for the base case NMA and sensitivity analyses are consistent: ixekizumab, brodalumab, secukinumab, infliximab, ustekinumab, adalimumab, etanercept, apremilast, DMF, placebo.

The ERG considers the company's economic model to meet the requirements of the NICE reference case and to be of high-quality generally. The company base case and sensitivity analysis scenarios were successfully reproduced by the ERG in deterministic and probabilistic analyses. Basic logical tests performed by the ERG showed the model behaved logically. The ERG conducted its own validation of the model and coding and concluded that the model functioned correctly and model inputs were found to match those reported of the submission with one minor exception that had no noticeable impact on the final results.

Despite the strengths of the company submission, 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.

The key uncertainties identified by the ERG were explored in 12 separate scenarios. An alternative ERG base-case was also undertaken combining changes based on 6 of the 12 separate scenarios. The specific scenarios represented those scenarios the ERG consider provide more appropriate or plausible assumptions than the company base-case.

The most efficient sequences identified in the ERG alternative base-case are identical to those derived from the company base-case model. The ERG consider that this provides significant reassurance and confirmation regarding the robustness of the company's results. However, these results exclude the confidential PAS schemes for several comparators (ixekizumab, secukinumab and apremilast). The impact of including these confidential PAS schemes is presented in a separate confidential appendix.

8.1 Implications for research

The ERG's exploratory cost-effectiveness analyses identified two potential areas of uncertainty which potentially warrant further research. Firstly, the utility values reported for brodalumab based on EQ-5D-3L were markedly different to those previously reported for ixekizumab by Picard et al (2017) based on EQ-5D-5L.[60] This may indicate important differences in the trial population characteristics. Equally it may indicate potentially important differences in the properties of the 3L and 5L variants of the EuroQoL-5D instrument. The differences in utility values based on the different variants have potentially important implications for the cost-effectiveness of existing and future biological treatments for psoriasis. Further research would be valuable to further explore the reason for these differences and to help determine the most appropriate instrument for individuals with moderate to severe psoriasis.

Secondly, the ERG's exploratory analyses highlighted the importance of longer term discontinuation as a potential driver of the cost-effectiveness results. Evidence is emerging from longer-term registries (e.g. BADBIR) which indicate that they may be important differences both within classes and across different classes. These differences have the potential to have important implications for longer-term cost-effectiveness estimates. Currently there is more limited longer-term evidence for the IL-17 inhibitors given their more recent marketing authorisations. However, it will be important to continue to assess the longer-term durability of these treatments to ensure that the higher-initial efficacy that seems to be evident is also reflected in improved longer-term durability.

9 References

1. National Institute for Health and Care Excellence. *Psoriasis: assessment and management*. 2012. Available from: https://www.nice.org.uk/guidance/cg153 [accessed 13th November 2017].

2. Springate DA, Parisi R, Kontopantelis E, Reeves D, Griffiths CE, Ashcroft DM. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. *Br J Dermatol* 2017;**176**:650-8.

3. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, 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**:826-50.

4. Leino M, Mustonen A, Mattila K, Koulu L, Tuominen R. Influence of psoriasis on household chores and time spent on skin care at home: a questionnaire study. *Dermatol Ther (Heidelb)* 2015;**5**:107-16.

5. 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**:280-4.

6. Lynde CW, Poulin Y, Guenther L, Jackson C. The burden of psoriasis in Canada: insights from the pSoriasis Knowledge IN Canada (SKIN) survey. *J Cutan Med Surg* 2009;**13**:235-52.

7. Gowda S, Goldblum OM, McCall WV, Feldman SR. Factors affecting sleep quality in patients with psoriasis. *J Am Acad Dermatol* 2010;**63**:114-23.

8. Anstey A, McAteer H, Kamath N, Percival F. Extending psychosocial assessment of patients with psoriasis in the UK, using a self-rateds, web-based survey. *Clin Exp Dermatol* 2012;**37**:735-40.

9. Ljosaa TM, Rustoen T, Mork C, Stubhaug A, Miaskowski C, Paul SM, et al. Skin pain and discomfort in psoriasis: an exploratory study of symptom prevalence and characteristics. *Acta Derm Venereol* 2010;**90**:39-45.

10. Feldman S, Zhao Y, Shi L, Tran M. Economic and comorbidity burden among patients with moderate-to-severe psoriasis. *J Manag Care Spec Pharm* 2015;**21**:874-88.

11. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GBE, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *J Invest Dermatol* 2015;**135**:984-91.

12. Mehta NN, Yu Y, Pinnelas R, Krishnamoorthy P, Shin DB, Troxel AB, et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. *Am J Med* 2011;**124**:775 e1-6.

13. Gelfand JM, Troxel A, Lewis J, Kurd S, Shin D, Wang X, et al. The risk of mortality in patients with psoriasis results from a population-based study. *Arch Dermatol* 2007;**143**:1493-9.

14. Kurd S, Troxel A, Crits-Christoph P, Gelfand J. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. *Arch Dermatol* 2010;**146**:891-5.

15. National Institute for Health and Care Excellence. *Topical therapy for psoriasis*. NICE; 2017. Available from: http://pathways.nice.org.uk/pathways/psoriasis [accessed 13th November 2017].

16. National Institute for Health and Care Excellence. *Systemic biological therapy for psoriasis*. NICE; 2017. Available from: http://pathways.nice.org.uk/pathways/psoriasis [accessed 13th November 2017].

17. National Institute for Health and Care Excellence. *Systemic non-biological therapy for psoriasis*. NICE; 2017. Available from: http://pathways.nice.org.uk/pathways/psoriasis [accessed 13th November 2017].

18. Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *Br J Dermatol* 2009;**161**:987-1019.

19. Malakouti M, Jacob SE, Anderson NJ. Treatment challenges in the management of moderate-to-severe plaque psoriasis - role of secukinumab. *Clin Cosmet Investig Dermatol* 2016;**9**:347-55.

20. Carrascosa JM, van Doorn MB, Lahfa M, Nestle FO, Jullien D, Prinz JC. Clinical relevance of immunogenicity of biologics in psoriasis: implications for treatment strategies. *J Eur Acad Dermatol Venereol* 2014;**28**:1424-30.

21. 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.

22. 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**:244-52.

23. Papp KA, Reid C, Foley P, Sinclair R, Salinger DH, Williams G, et al. Anti-IL-17 receptor antibody AMG 827 leads to rapid clinical response in subjects with moderate to severe psoriasis: results from a phase I, randomized, placebo-controlled trial. *J Invest Dermatol* 2012;**132**:2466-9.

24. Eedy DJ, Griffiths CEM, Chalmers RJG, Ormerod AD, Smith CH, Barker JNWN, et al. Care of patients with psoriasis: an audit of U.K. services in secondary care. *Br J Dermatol* 2009;**160**:557-64.

25. Geale K, Henriksson M, Schmitt-Egenolf M. Evaluating equality in psoriasis healthcare: a cohort study of the impact of age on prescription of biologics. *Br J Dermatol* 2016;**174**:579-87.

26. Nakagawa H, Niiro H, Ootaki K. 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**:44-52.

27. Papp K, Leonardi C, Menter A, Ortonne J-P, Krueger J, Kricorian G, et al. Brodalumab, an anti–interleukin-17–receptor antibody for psoriasis. *N Engl J Med* 2012;**366**:1181-9.

28. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013*. NICE; 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 [accessed 13th November 2017].

29. Amgen Inc. *A Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-2 (Clinical Study Report)*; 2015.

30. Amgen Inc. *Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-3 (Clinical Study Report)*; 2015.

31. 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**:1318-28.

32. 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**:273-86.

33. Amgen Inc. *A Phase 3 Study to Evaluate the Efficacy, Safety, and Effect of Withdrawal and Retreatment With Brodalumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-1 (Clinical Study Report)*; 2015.

34. Amgen Inc. *Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-3 (Clinical Study Report)*; 2016.

35. Valeant Pharmaceuticals North America. *Brodalumab. Dermatoligic and Ophthalmic Drugs Advisory Committee*.

36. *Brodalumab: Summary of Product Characteristics*; 2017 May.

37. Shikiar R, Willian MK, Okun MM, Thompson CS, Revicki DA. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. *Health Qual Life Outcomes* 2006;**4**:71.

38. Amgen Inc. *A Phase 3 Study to Evaluate the Efficacy and Safety of Induction and Maintenance Regimens of Brodalumab Compared With Placebo and Ustekinumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-2 (Clinical Study Report)*; 2016.

39. Amgen Inc. *A Phase 3 Study to Evaluate the Efficacy, Safety, and Effect of Withdrawal and Retreatment With Brodalumab in Subjects With Moderate to Severe Plaque Psoriasis: AMAGINE-1 (Clinical Study Report)*; 2016.

40. European Medicines Agency. *Assessment report. Kyntheum. International non-proprietary name: broadalumab. Procedure no. EMEA/H/C/003959/0000*. London: EMA; 2017.

41. Conti HR, Gaffen SL. IL-17-mediated immunity to the opportunistic fungal pathogen Candida albicans. *J Immunol* 2015;**195**:780-8.

42. FDA. Clinical Outcome Assessment Review - Ixekizumab. 2016 [Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125521Orig1s000MedR.pdf. Accessed: 16 December 2016.]

43. Valeant Pharmaceuticals North America. *BRODALUMAB injection. Food and Drug Administration. Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC). Meeting Date: July 19, 2016*; 2016. Available from: https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/dermatologicandophthalmicdrugsadvisorycommittee/ucm511360.pdf

44. Valeant Pharmaceuticals North America. *BRODALUMAB injection Food and Drug Administration. Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC). Meeting Date: July 19, 2016. Errata to Sponsor Briefing Document*; 2016. Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM511358.pdf

45. Food and Drug Administration. Centre for Drug Evaluation and Research. *Background Package for BLA 761032 Siliq (brodalumab) injection, 210 mg/1.5 ml*; 2016. Available from: https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/dermatologicandophthalmicdrugsadvisorycommittee/ucm511357.pdf

46. National Institute for Health and Care Excellence. *Ixekizumab for treating moderate to severe plaque psoriasis [ID904]. Committee papers*. NICE; 2016. Available from: https://www.nice.org.uk/guidance/ta442/documents/committee-papers-3 [accessed 13th November 2017].

47. National Institute for Health and Care Excellence. *Dimethyl fumarate for treating moderate to severe plaque psoriasis [TA475]*. NICE; 2017. Available from: https://www.nice.org.uk/guidance/ta475 [accessed 13th November 2017].

48. National Institute for Health and Care Excellence. *Apremilast moderate to severe - psoriasis (rapid review of TA368) [ID987]*. NICE; 2016. Available from: https://www.nice.org.uk/guidance/ta419/ [accessed 13th November 2017].

49. British Association of Dermatologists. *Guidelines for biologic therapy for psoriasis: methods, evidence and recommendations*. London; 2017.

50. Dias S, Welton NJ, Sutton AJ, Ades AE. *A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials* In: NICE DSU Technical Support Document 2; 2011; last updated September 2016. Available from: http://www.nicedsu.org.uk

51. Dias S, Sutton AJ, Welton NJ, Ades AE. *Heterogeneity: subgroups, meta-regression, bias and bias-adjustment*. In: NICE DSU Technical Support Document 3; 2011; last updated April 2012. Available from: http://www.nicedsu.org.uk

52. Signorovitch J, Betts K, Yan Y, LeReun C, Sundaram M, Wu E, et al. Comparative efficacy of biological treatments for moderate-to-severe psoriasis: a network meta-analysis adjusting for cross-trial differences in reference arm response. *Br J Dermatol* 2015;**172**:504-12.

53. Cooper N, Sutton A, Morris D, Ades A, Welton N. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. *Stat Med* 2009;**28**:1861-81.

54. National Institute for Health and Care Excellence. *Secukinumab for the treatment of moderate to severe plaque psoriasis [TA350]*. In: Single Technology Appraisal. London: NICE; 2015.

55. National Institute for Health and Care Excellence. *Adalimumab for the treatment of adults with psoriasis*; 2008. Available from: https://www.nice.org.uk/guidance/ta146/chapter/1-Guidance

56. National Institute for Health and Care Excellence. *Apremilast for treating moderate to severe plaque psoriasis [TA419]* NICE; 2016. Available from: https://www.nice.org.uk/guidance/ta419/ [accessed 13th November 2017].

57. National Institute for Health and Care Excellence. *Etanercept and efalizumab for the treatment of adults with psoriasis*. London: NICE; 2016. Available from: https://www.nice.org.uk/guidance/ta103

58. National Institute for Health and Care Excellence. *Infliximab for the treatment of adults with psoriasis. Technology appraisal guidance TA134*. In: Technology appraisal guidance; 2008. Available from: https://www.nice.org.uk/guidance/ta134

59. National Institute for Health and Care Excellence. *Ustekinumab for the treatment of adults with moderate to severe psoriasis*; 2009. Available from: https://www.nice.org.uk/guidance/ta180

60. 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**:19-27.

61. van Hout B, Janssen M, Feng Y, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;**15**:708-15.

62. National Institute for Health and Care Excellence. *Ixekizumab for treating moderate to severe plaque psoriasis. Technology appraisal guidance [TA442]*. In. London: NICE; 2017. Available from: https://www.nice.org.uk/guidance/ta442

63. 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.

64. Stinnett A, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998;**18**:S68-80.

10 Appendices

10.1 ERG revisions to NMA

The ERG's revisions to the Bayesian NMA for PASI utilised the same underlying framework of analysis used by the company to evaluate the probability of PASI responses in different categories of PASI thresholds 50/75/90/100 within a single model. This single synthesis multinomial model with a probit link assumes that there is an underlying continuous variable which has been categorised by specifying the cut-offs. It assumes also that the treatment effect is the same regardless of the different cut-offs in each trial. All PASI response models were run for 50,000 iterations after a burn-in of 20,000 on 3 chains. The synthesis model results provide pooled probabilities of achieving PASI 50, 75, 90 and 100 for each treatment of interest, alongside a measure of uncertainty, i.e. 95% credibility intervals.

In brief, trials reported r_{ikj}, the number of patients in arm k of trial i belonging to different, mutually exclusive categories j = 1, 2, 3, 4 , where these categories represent the different thresholds of PASI score (50%, 75%, 90% or 100% improvement). The responses for each arm k of trial i in category j follows a multinomial distribution as $r_{i,k,j=1,\dots,J} \sim Multinomial\left(p_{i,k,j=1,\dots,J}, n_{i,k}\right)\ with\ \sum_{j=1}^{J} p_{i,k,j} = 1$,which has been parameterised as a series of conditional binomial distributions, with parameters of interest, the probabilities p_{ikj}, that a patient in arm k (k = 1, 2, 3, 4) of trial i (i = 1,….., NS – where NS is the number of studies) belongs to category j (j = 1, 2, 3, 4). A probit link function was used, the inverse of the normal cumulative distribution function Φ, to define the p_{ikj} as a function of a set of threshold values, z_j. The threshold values (estimated within the model) are such that the probability that the standard normal (the probit score) will take a value less than or equal to z_1 will reflect the probability of obtaining a PASI response lower than 50%, that is, *1-PASI50*. The probability that the standard normal will take a value less than or equal to z_2 will reflect the probability of obtaining a PASI response lower than 75%, that is, *1-PASI75*, and analogously, for z_3 and z_4. Placebo and treatments assumed to shift the mean of the distribution. This means that the pooled effect of taking the experimental treatment instead of the control is to change the probit score (or *Z score*) of the control arm, by $d_{i,1}$ standard deviations. Therefore, the model is written as $p_{ikj}=\Phi(\mu_i+z_j+\delta_{i,1k}\, I_{\{k\neq 1\}})$. The terms z_j are the differences on the standard normal scale between the response to category j and the response to category *j-1* in all the arms of trial i. The baselines, μ_i, were trial-specific (i.e. unconstrained) and were given non-informative priors. A non-informative prior was assign to the treatment effects parameter (δ_k). A uniform prior was assign to the parameter z_j. The correlation structure induced by multi-arm trials was accounted for.

Placebo adjustment

An alternative NMA model to the one described above is an NMA meta-regression model on baseline risk (i.e. placebo response) - the ERG's preferred model. The meta-regression model on baseline risk imposes a common interaction effect between baseline risk and relative effectiveness that account for variation in reference arm response across trials. The common interaction assumption is the least data demanding (i.e. only one extra parameter is needed to be estimated), but it also imposes the strongest assumption as it implies that the same placebo effect exists across evaluated interventions (excluding placebo).[53]

Following the principles outlined in NICE DSU TSD3[51] and in Signorovitch et al[52], the baseline risk for each study, μ_i, is on the same scale as the linear predictor. The mean baseline risk for centring, μ^*, is required to be on similar scale and is derived from all trials that include treatment 1 (i.e. reference treatment, placebo). No baseline risk adjustment is performed for trials which do not include the reference treatment. Thus, the placebo adjusted model is written as $p_{ikj}=\Phi(\mu_i+z_j+(\delta_{i,1k}+(\beta_{1ti k}-\beta_{1ti1})(\mu_i-\mu^*))\, I_{\{k\neq 1\}})$. Where, $\beta_{11}=0$, $\beta_{1k}=B$ ($k=2,\ldots,NT$ – where NT is the number of treatments) for all treatments.

To estimate the mean baseline risk for centring, μ^*, the placebo adjusted model described in the CS averaged across all trials included in the NMA model (*mx <- mean(mu[])*). This approach is reasonable when the trials considered by the NMA model are placebo trials (i.e. the trial reference arm is placebo). When a proportion of the included trials do not include placebo, an external estimation of μ^* may be required.

In addition, and compared to the placebo-adjusted model described in the CS, the ERG placebo adjusted synthesis model considered the following changes:

1. The treatment effect contrast (*delta[i,1]*) in the model description was dropped as contrasts are estimated when defining the random effect (*md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]*); and
2. True uninformative priors were given to μ and B.

The WinBUGS code for the ERG synthesis model with placebo adjustment and external estimation of μ^* is provided below. ERG changes, to the code presented in the CS, are highlighted in bold.

Mathematical description of placebo adjusted model and underlying assumptions for PASI response

Likelihood $r_{ikj} \sim Binomial(p_{ikj} n_{ikj})$ *Model* $q_{ikj} = 1 - (p_{ikC_{i,j+1}} / p_{ikC_{i,j}})$ $\theta_{ikj} = \mu_i + \delta_{t_{i,k}} - \delta_{t_{i,1}} + z_j + \beta(\mu_i - \mu^*)$ $p_{ikC_{ij}} = 1 - AD_{ikj}$ $AD_{ikj} = \phi(\theta_{ik,j-1})$ $\delta_t \sim dnorm(d_t, \sigma^2)$ Priors $\sigma \sim dunif(0,2)$ $\mu_i \sim dnorm(0,0.00001)$ $\beta \sim dnorm(0,0.00001)$ $z_j \sim dunif(0,2)$	*Assumptions:* • Unconstrained baselines • Independent treatment effects • Random effects between studies • Fixed effect for each of the *j-1* categories over all trials • Common interaction term between studies (placebo effect adjustment, β)

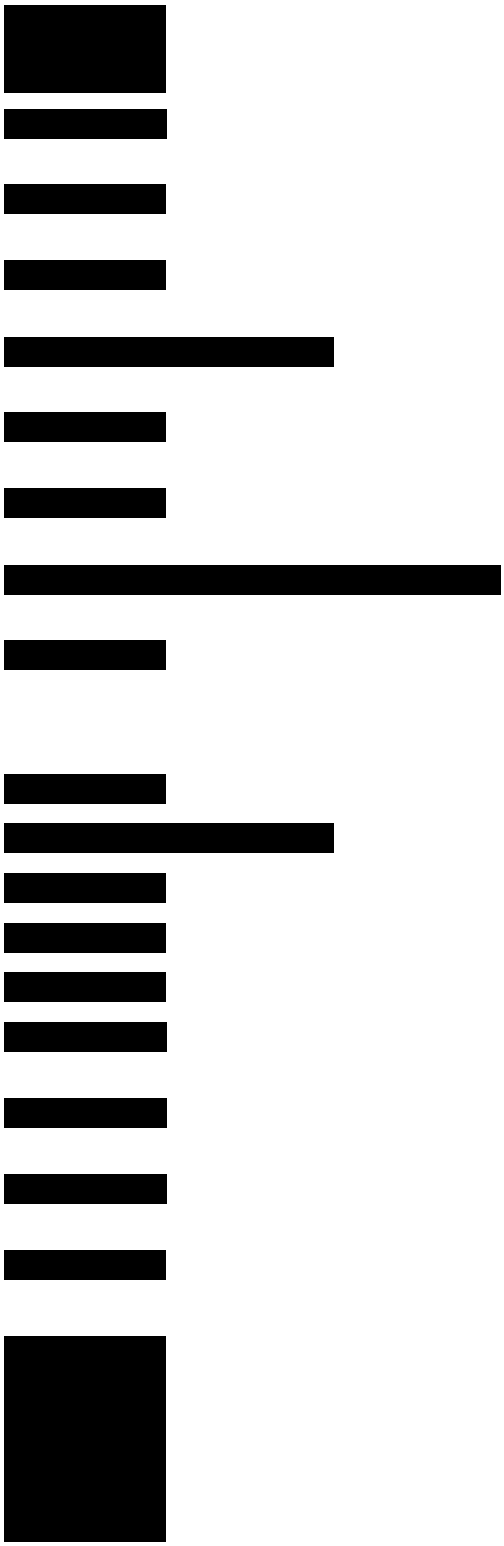
Predictions of absolute effects for all treatment contrasts

Predictions of absolute effects (PASI 50/75/90/100 responses) for all treatment contrasts were perfomed using T_{jt}=1-Φ($A+\delta_t+z_j+(B)I_{\{k\neq 1\}}$) where δ_k are treatment effects for each k, z_j the threshold values for each PASI category j, B the common regression (slope) coefficient relating to the placebo adjustment and A is the pooled baseline effect (i.e. on reference treatment) on the probit scale obtained from external sources.

In the CS, PASI 50 response outcomes for placebo from included studies were used to inform the baseline event rates and estimated through separate Bayesian analysis in WinBUGS. The ERG agrees with the approach used in the submission. However, the ERG implemented further analyses by considering data on baseline risk from the AMAGINE trials more explicitly towards the estimation of A, as described in section 4.4.1.

WinBUGS code for placebo adjustment model (ERG revisions to code in bold):

[redacted]



[redacted]

[redacted]

[redacted]

10.2 Quality checklist for company economic model

Was a well-defined question posed in answerable form?	The decision problem is clearly stated, although not in line with the NICE scope. However, the positioning of brodalumab, which determines the range of comparators and the relevant population, appears consistent with current treatment pathways and previous appraisals. The model perspective is in line with the NICE reference case.
Was a comprehensive description of the competing alternatives given?	All relevant comparators have been included in the evaluation but not all possible sequences have been evaluated for reasons of feasibility.
Was the effectiveness of the programmes or services established?	Data concerning the effectiveness for brodalumab come from the AMAGINE clinical trials. Effectiveness data for brodalumab and its comparators was synthesised using a NMA, with search strategies and inclusion/exclusion criteria appropriately chosen.
Were all the important and relevant costs and consequences for each alternative identified? Were they measured accurately? Were they valued credibly? Were they adjusted for differential timing?	Resource use and costs were identified appropriately and followed established practice (e.g., BSC from Fonia) and clinical guidelines (e.g. monitoring frequency from BAD Guidelines). The most relevant cost categories for evaluation were considered. Health effects were expressed as QALYs using EQ-5D data collected as part of the AMAGINE-1 trial. A disutility multiplier was employed to account for the effect of adverse events. A discrepancy is noted between the use of DLQI>10 population for health gains and the ITT population for treatment effectiveness. The regression used to compute health gains did not control for baseline EQ-5D, which was deemed to be the most appropriate regression and was included in the ERG base case. Both costs and QALYs were adjusted for differential timing.
Was an incremental analysis of costs and consequences of alternative performed? Was uncertainty in the estimates of costs and consequences adequately characterized?	Incremental analysis of costs and consequences were performed. Results have been reported both as a fully incremental analysis and as a pair-wise analysis across the different evaluated sequences. Uncertainty has been adequately characterized by undertaking a series one-way deterministic sensitivity analyses, as well as 1000 probabilistic sensitivity analyses. A series of scenarios investigated several important assumptions.
Did the presentation and discussion of study results include all issues of concerns to users?	The company reported all results relative to the evaluation of treatment sequences, with DMF as the referent comparator. The ERG considers that the use of net-benefit calculations and associated

	rankings of each individual treatment versus BSC could provide additional insights given the restrictive nature of the sequences evaluated.

10.3 ERG exploratory analyses – excluding confidential PAS for comparators

ERG Exploratory Analysis 1 (company base-case assumptions) - Incremental net-benefit and rankings

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Rank @20k	INB vs BSC @30k	Rank @30k
BSC	10.67	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.81	£113,873	1.14	£14,236	£12,540	£8,468	**1**	£19,821	**1**
Dimethyl fumarate	10.90	£98,899	0.23	-£737	Dominant	£5,238	**2**	£7,489	4
Adalimumab	11.50	£112,695	0.83	£13,058	£15,816	£3,454	**3**	£11,710	**3**
Apremilast	10.99	£102,705	0.32	£3,069	£9,479	£3,406	4	£6,643	6
Ustekinumab	11.57	£114,617	0.90	£14,981	£16,714	£2,945	5	£11,908	**2**
Etanercept 50 mg per week	11.13	£106,087	0.46	£6,451	£13,903	£2,829	6	£7,469	5
Infliximab	11.66	£129,759	0.99	£30,122	£30,460	-£10,344	7	-£455	7
Secukinumab	11.74	£139,036	1.07	£39,400	£36,969	-£18,085	8	-£7,427	9
Ixekizumab	11.84	£141,502	1.17	£41,865	£35,695	-£18,408	9	-£6,679	8

ERG Exploratory Analysis 2 (effect modification) - Incremental net-benefit and rankings

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	10.67	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.58	£111,373	0.91	£11,736	£12,840	£6,545	**1**	£15,685	1
Dimethyl fumarate	10.85	£98,966	0.18	-£671	Dominant	£4,262	**2**	£6,057	4
Apremilast	10.93	£102,260	0.26	£2,623	£10,123	£2,559	**3**	£5,151	6
Adalimumab	11.33	£110,573	0.66	£10,937	£16,475	£2,340	4	£8,979	**3**
Etanercept 50 mg per week	11.04	£105,023	0.37	£5,387	£14,452	£2,068	6	£5,795	5
Ustekinumab	11.39	£112,271	0.72	£12,634	£17,526	£1,783	5	£8,992	**2**
Infliximab	11.47	£124,940	0.80	£25,304	£31,777	-£9,378	7	-£1,415	7
Secukinumab	11.53	£132,625	0.86	£32,988	£38,447	-£15,828	8	-£7,247	9
Ixekizumab	11.61	£134,722	0.94	£35,085	£37,150	-£16,197	9	-£6,753	8

ERG Exploratory Analysis 3: ERG revisions to Winbugs code with placebo-adjustment (baseline placebo response derived from all trials in NMA)

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	10.60	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.75	£113,865	1.15	£14,229	£12,393	**£8,734**	**1**	**£20,216**	**1**
Dimethyl fumarate	10.96	£98,717	0.36	-£919	Dominant	**£8,053**	**2**	£11,620	4
Apremilast	10.98	£103,005	0.37	£3,368	£9,015	**£4,105**	**3**	£7,841	5
Adalimumab	11.48	£113,164	0.88	£13,528	£15,443	£3,992	4	**£12,752**	**2**
Ustekinumab	11.50	£114,437	0.89	£14,800	£16,577	£3,056	5	**£11,984**	**3**
Etanercept 50 mg per week	11.06	£105,954	0.46	£6,317	£13,776	£2,854	6	£7,440	6
Infliximab	11.59	£129,490	0.99	£29,853	£30,194	-£10,079	7	-£192	7
Secukinumab	11.65	£138,090	1.04	£38,453	£36,885	-£17,603	8	-£7,178	9
Ixekizumab	11.76	£140,834	1.16	£41,197	£35,562	-£18,028	9	-£6,443	8

ERG Exploratory Analysis 4: ERG revisions to Winbugs code with placebo-adjustment (baseline placebo response derived from AMAGINE-1 only)

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	10.35	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.51	£113,527	1.16	£13,890	£11,957	**£9,343**	**1**	**£20,960**	**1**
Dimethyl fumarate	10.68	£98,782	0.33	-£854	Dominant	**£7,434**	**2**	£10,725	4
Adalimumab	11.21	£112,506	0.86	£12,870	£14,959	**£4,337**	**3**	**£12,941**	**2**
Apremilast	10.69	£102,689	0.35	£3,053	£8,835	£3,858	4	£7,313	5
Ustekinumab	11.23	£113,775	0.88	£14,139	£16,091	£3,435	5	**£12,221**	**3**
Etanercept 50 mg per week	10.78	£105,386	0.43	£5,749	£13,379	£2,845	6	£7,142	6
Infliximab	11.33	£128,464	0.99	£28,828	£29,247	-£9,115	7	£742	7
Secukinumab	11.39	£136,889	1.04	£37,253	£35,697	-£16,381	8	-£5,945	9
Ixekizumab	11.52	£139,977	1.17	£40,341	£34,373	-£16,869	9	-£5,132	8

ERG Exploratory Analysis 5: ERG revisions to Winbugs code with placebo-adjustment (baseline placebo response derived from AMAGINE-2/3 only)

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	10.76	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.89	£113,999	1.13	£14,362	£12,704	**£8,248**	**1**	**£19,554**	**1**
Dimethyl fumarate	11.13	£98,688	0.36	-£948	Dominant	**£8,233**	**2**	**£11,875**	**3**
Apremilast	11.14	£103,145	0.38	£3,508	£9,209	**£4,111**	**3**	£7,921	5
Adalimumab	11.63	£113,433	0.87	£13,797	£15,818	£3,648	4	**£12,370**	**2**
Etanercept 50 mg per week	11.23	£106,216	0.47	£6,579	£14,105	£2,750	5	£7,414	6
Ustekinumab	11.65	£114,719	0.89	£15,082	£16,961	£2,703	6	£11,596	4
Infliximab	11.74	£129,930	0.98	£30,294	£30,902	-£10,688	7	-£885	7
Secukinumab	11.79	£138,601	1.03	£38,964	£37,762	-£18,328	8	-£8,009	9
Ixekizumab	11.90	£141,191	1.14	£41,554	£36,421	-£18,735	9	-£7,326	8

ERG Exploratory Analysis 6: Utility regression adjusting for baseline EQ-5D (DLQI>10 subgroup)

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	10.59	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.80	£113,873	1.21	£14,236	£11,742	**£10,012**	**1**	**£22,137**	**1**
Dimethyl fumarate	10.85	£98,899	0.26	-£737	Dominant	**£5,894**	**2**	£8,472	5
Adalimumab	11.49	£112,695	0.91	£13,058	£14,429	**£5,042**	**3**	**£14,092**	**3**
Ustekinumab	11.56	£114,617	0.98	£14,981	£15,328	£4,566	4	**£14,340**	**2**
Apremilast	10.96	£102,705	0.37	£3,069	£8,340	£4,290	5	£7,969	6
Etanercept 50 mg per week	11.11	£106,087	0.52	£6,451	£12,377	£3,973	6	£9,185	4
Infliximab	11.66	£129,759	1.07	£30,122	£28,196	-£8,756	7	£1,928	7
Secukinumab	11.73	£139,036	1.15	£39,400	£34,408	-£16,498	8	-£5,048	9
Ixekizumab	11.84	£141,502	1.25	£41,865	£33,535	-£16,897	9	-£4,413	8

ERG Exploratory Analysis 7: Utility regression adjusting for baseline EQ-5D (ITT population)

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	11.95	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	12.94	£113,873	0.99	£14,236	£14,384	**£5,559**	**1**	**£15,456**	**1**
Dimethyl fumarate	12.16	£98,899	0.21	-£737	Dominant	**£4,882**	**2**	£6,954	4
Apremilast	12.24	£102,705	0.30	£3,069	£10,356	**£2,858**	**3**	£5,821	6
Etanercept 50 mg per week	12.37	£106,087	0.42	£6,451	£15,315	£1,973	4	£6,185	5
Adalimumab	12.68	£112,695	0.74	£13,058	£17,762	£1,645	5	**£8,997**	**2**
Ustekinumab	12.74	£114,617	0.80	£14,981	£18,843	£920	6	**£8,870**	**3**
Infliximab	12.82	£129,759	0.87	£30,122	£34,607	-£12,714	7	-£4,010	7
Secukinumab	12.88	£139,036	0.93	£39,400	£42,181	-£20,718	8	-£11,378	9
Ixekizumab	12.97	£141,502	1.02	£41,865	£41,061	-£21,473	9	-£11,277	8

ERG Exploratory Analysis 8: External utility estimates: EQ-5D-3L crosswalk values reported for ixekizumab

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	13.24	£99,637	NA	NA	NA	NA	NA	NA	NA
Dimethyl fumarate	13.35	£98,899	0.11	-£737	Dominant	£2,872	**1**	£3,939	**1**
Apremilast	13.39	£102,705	0.15	£3,069	£20,073	-£11	**2**	£1,518	**2**
Etanercept 50 mg per week	13.46	£106,087	0.22	£6,451	£29,655	-£2,100	**3**	£75	4
Brodalumab	13.76	£113,873	0.52	£14,236	£27,551	-£3,902	4	£1,265	**3**
Adalimumab	13.62	£112,695	0.38	£13,058	£34,243	-£5,431	5	-£1,618	5
Ustekinumab	13.65	£114,617	0.41	£14,981	£36,231	-£6,711	6	-£2,576	6
Infliximab	13.69	£129,759	0.45	£30,122	£66,590	-£21,075	7	-£16,552	7
Secukinumab	13.73	£139,036	0.49	£39,400	£80,870	-£29,656	8	-£24,784	8
Ixekizumab	13.77	£141,502	0.53	£41,865	£78,547	-£31,205	9	-£25,875	9

.

ERG Exploratory Analysis 9: Adjustment to brodalumab dosing assumptions

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	10.67	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.81	[redacted]	1.14	[redacted]	[redacted]	[redacted]	**1**	[redacted]	**1**
Dimethyl fumarate	10.90	£98,899	0.23	-£737	Dominant	£5,238	**2**	£7,489	4
Adalimumab	11.50	£112,695	0.83	£13,058	£15,816	£3,454	**3**	£11,710	**3**
Apremilast	10.99	£102,705	0.32	£3,069	£9,479	£3,406	4	£6,643	6
Ustekinumab	11.57	£114,617	0.90	£14,981	£16,714	£2,945	5	£11,908	**2**
Etanercept 50 mg per week	11.13	£106,087	0.46	£6,451	£13,903	£2,829	6	£7,469	5
Infliximab	11.66	£129,759	0.99	£30,122	£30,460	-£10,344	7	-£455	7
Secukinumab	11.74	£139,036	1.07	£39,400	£36,969	-£18,085	8	-£7,427	9
Ixekizumab	11.84	£141,502	1.17	£41,865	£35,695	-£18,408	9	-£6,679	8

ERG Exploratory Analysis 10: Inclusion of non-responder costs

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	10.67	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.81	£113,959	1.14	£14,322	£12,616	£8,382	**1**	£19,735	**1**
Dimethyl fumarate	10.90	£99,677	0.23	£40	£178	£4,461	**2**	£6,711	5
Adalimumab	11.50	£113,023	0.83	£13,386	£16,213	£3,126	**3**	£11,382	**3**
Apremilast	10.99	£103,405	0.32	£3,769	£11,642	£2,706	4	£5,943	6
Ustekinumab	11.57	£114,897	0.90	£15,261	£17,027	£2,665	5	£11,628	**2**
Etanercept 50 mg per week	11.13	£106,528	0.46	£6,891	£14,853	£2,388	6	£7,028	4
Infliximab	11.66	£129,885	0.99	£30,248	£30,587	-£10,470	7	-£580	7
Secukinumab	11.74	£139,155	1.07	£39,518	£37,080	-£18,203	8	-£7,546	9
Ixekizumab	11.84	£141,572	1.17	£41,935	£35,754	-£18,478	9	-£6,749	8

.

ERG Exploratory Analysis 11: Inclusion of additional monitoring costs for DMF

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	10.67	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.81	£113,873	1.14	£14,236	£12,540	£8,468	**1**	£19,821	**1**
Dimethyl fumarate	10.90	£99,261	0.23	-£375	Dominant	£4,876	**2**	£7,126	6
Adalimumab	11.50	£112,695	0.83	£13,058	£15,816	£3,454	**3**	£11,710	**3**
Apremilast	10.99	£102,705	0.32	£3,069	£9,479	£3,406	4	£6,643	5
Ustekinumab	11.57	£114,617	0.90	£14,981	£16,714	£2,945	5	£11,908	**2**
Etanercept 50 mg per week	11.13	£106,087	0.46	£6,451	£13,903	£2,829	6	£7,469	4
Infliximab	11.66	£129,759	0.99	£30,122	£30,460	-£10,344	7	-£455	7
Secukinumab	11.74	£139,036	1.07	£39,400	£36,969	-£18,085	8	-£7,427	9
Ixekizumab	11.84	£141,502	1.17	£41,865	£35,695	-£18,408	9	-£6,679	8

ERG Exploratory Analysis 12: Lower withdrawal for ustekinumab only

Drug (1 line only)	Total QALYs	Total costs	Incremental QALYs vs BSC	Incremental costs vs BSC	pairwise ICER vs BSC	INB vs BSC @20k	Ranking @20k	INB vs BSC @30k	Ranking @30k
BSC	10.67	£99,637	NA	NA	NA	NA	NA	NA	NA
Brodalumab	11.81	£113,873	1.14	£14,236	£12,540	£8,468	**1**	£19,821	**2**
Ustekinumab	12.46	£127,656	1.79	£28,019	£15,677	£7,727	**2**	£25,601	**1**
Dimethyl fumarate	10.90	£98,899	0.23	-£737	Dominant	£5,238	**3**	£7,489	4
Adalimumab	11.50	£112,695	0.83	£13,058	£15,816	£3,454	4	£11,710	**3**
Apremilast	10.99	£102,705	0.32	£3,069	£9,479	£3,406	5	£6,643	6
Etanercept 50 mg per week	11.13	£106,087	0.46	£6,451	£13,903	£2,829	6	£7,469	5
Infliximab	11.66	£129,759	0.99	£30,122	£30,460	-£10,344	7	-£455	7
Secukinumab	11.74	£139,036	1.07	£39,400	£36,969	-£18,085	8	-£7,427	9
Ixekizumab	11.84	£141,502	1.17	£41,865	£35,695	-£18,408	9	-£6,679	8

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Brodalumab for treating moderate to severe plaque psoriasis [ID878]

You are asked to check the ERG report from the Centre for Reviews and Dissemination and Centre for Health Economics, 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 the end of **5 December** 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Accuracy of reported trial data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13. "Across the three AMAGINE trials withdrawal rates in patients treated with the 210 mg Q2W dose were low with around 88% completing the study to week 52. The ERG notes this is comparable with the drug survival rates published for other biologics."	The 88% figure refers to all patients on brodalumab, including the 140mg dose. For patients just receiving brodalumab 210mg the figure is 81-82%	The amendment will aid accuracy.	Amendment made (pages 13, 54 and 67).
Page 37. "However, the difference in PASI 75 response between brodalumab and ustekinumab was not statistically significant at week 12 in AMAGINE-2, as reported in the publication (P=0.08),31 although this was stated as NT (not tested) in Table 13 of the CS and reported as statistically significant in the text on page 47 of the CS" This is not factually clear. The non-significance value (P=0.08) specifically relates to the adjusted P value following 'sequence testing'. In this situation a failure of a prior endpoint in the sequence (in this case the PASI 100 results at the unlicensed 140mg dose) automatically defaults all further adjustments to the same value. However when you look at the 'nominal testing' P value- you will see that the results for PASI 75 at the 210mg dose is highly	The difference in PASI 75 response between brodalumab and ustekinumab was highly significant P= <0.001 at week 12 in AMAGINE-2 based on the nominal p-value (testing alone).The publication also reports that when looking at the adjusted P values based on "sequence testing" ,it was not statistically significant due to non-significance before the test of PASI-75 from the 140mg dose (P=0.08),31.	The amendment will aid clarity and accuracy.	The text on page 37 has been amended for clarity and accuracy.

significant. So the non-significance is really due to the sequence in the protocol defined testing and a non-significance occurrence before the test of PASI-75 between Broda 210 and Ustekinumab			

Issue 2 Confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13. "Some patients in the AMAGINE trials experienced SIB and overall there were [redacted] completed suicides.." The number of suicides is marked as commercial in confidence –however this number has been published in the FDA documents and Lebwohl SIB poster at AAD 2017 and discussed in the recent Lebwohl paper published Oct 2017	Remove confidentiality marking on the word "four"	Removing the CiC marking will assist transparency.	CIC marking removed on pages 13 and 53.

Issue 3 Generalisability of trial results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15. "The AMAGINE trials also excluded patients who had previously received ustekinumab or anti-IL-17 therapy, which may not be reflective of how brodalumab would be positioned in practice. Therefore,	Amend to read: "As was the case with clinical trials for other anti-IL-17 biologics, and in line with common practice for clinical trials for biologics,	The amendment is important in order to present a balanced view of the clinical evidence.	Not a factual inaccuracy. The final sentence about generalisability also relates

the results of the AMAGINE trials may not be entirely generalisable to the proposed eligible population." This statement is potentially misleading as it doesn't mention that this is the same case for the other biologics and in line with common practice for clinical trials more generally.	the AMAGINE trials also excluded patients who had previously received the active comparator (ustekinumab), or biologics which target the same pathway as brodalumab (anti-IL-17), which may not be reflective of how brodalumab would be positioned in practice.		to other inclusion/exclusion criteria (described earlier in the paragraph), not just patients who had received ustekinumab or anti-IL-17 therapy.
Page 31: "The clinical advisor to the ERG advised that older patients are often more ill than the general psoriasis population, so the exclusion of patients aged over 75 may have an impact on the generalisability of the trial results to the population seen in practice." This is factually accurate but not many patients would be expected to be seen with moderate-to-severe plaque psoriasis who are over 75. As the number would be small, it would not be expected to impact the generalisability of the trial results to clinical practice. Moreover, this is something that is also applicable to all clinical trials.		The amendment is important in order to present a balanced view of the clinical evidence.	Not a factual inaccuracy.
Page 32. "It is likely that patients eligible for brodalumab in NHS practice would have more severe or difficult to treat psoriasis so the efficacy of brodalumab seen in the trials may be higher than would be observed in clinical practice."		The amendment is important in order to present a balanced view of the clinical evidence.	Whilst patients in the AMAGINE trials had PASI 12 or above, the majority of patients had not received previous systemic therapy. Therefore, patients eligible for brodalumab in practice

We do not accept this statement as factually accurate. Patients enrolled on the AMAGINE studies had PASI 12 or above and patients in the NHS would be eligible for brodalumab with a PASI 10 or above.			may have more severe or difficult to treat psoriasis than in the trials. The sentence has been amended (page 32).

Issue 4 Incorrect references cited

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 53: "This is based on an independent analysis of SIB in trials of biological therapies for psoriasis conducted by the FDA.[42]" The manufacturer believes reference 42 in the reference list of the ERG report is incorrect, as it lists the approval letter for ixekizumab, rather than the independent review in which the subsequent data in the ERG report that is referenced to number 42 can be found: FDA. Clinical Outcome Assessment Review - Ixekizumab. 2016 [Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125521Orig1s000MedR.pdf. Accessed: 16 December 2016.]	Amend citation reference#42 to: FDA. Clinical Outcome Assessment Review - Ixekizumab. 2016 [Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125521Orig1s000MedR.pdf. Accessed: 16 December 2016.].	The amendment will aid accuracy.	Amended in reference list (page 133).

Issue 5 Incomplete information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 54. Section 4.2.3 includes the statement "Likewise, the EPAR report concludes that although current data does not establish causality, SIB are a potential risk with brodalumab." This unfairly omits to add the next sentence from the EPAR that give the statement context.	Add the following sentence from the EPAR: ""This potential risk is considered balanced with implemented information for the prescriber and the patient in the product information and will be followed up upon by means of a post authorisation safety study."	The statement in the ERG report is misleading by omitting important information that makes clear that the potential risk of SIB with brodalumab is balanced and is being explored further.	Amended on page 54.
Page 80. Section 5.2.3. Brodalumab is indicated "for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy". The word "patients" is omitted.	Amend this sentence to read: "Brodalumab is indicated for the treatment of moderate to severe plaque psoriasis in adult <u>patients</u> who are candidates for systemic therapy".	Amend to reflect indication wording as per SPC and stated in Table 2 (section B.1.2) of the company submission.	Amended on page 80.

Issue 6 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 100 -sentence before Table 25: The AMAGINE trials are incorrectly referred to as	Substitute AMAGINE for IMAGINE.	This amendment is important for the clarity and accuracy of the	Amended on page 100.

the IMAGINE trials.		ERG's report.	
Table 31-Summary of ERG exploratory scenarios: Brodalumab is spelt incorrectly.	Brodalumab to be spelled correctly throughout.	This amendment is important for the clarity and accuracy of the ERG's report.	Amended on page 121.