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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

FAST TRACK APPRAISAL (FTA)

Bimekizumab for treating moderate to severe plaque psoriasis [ID2692]

Appraisal Committee Meeting – 7 July 2021

1st Committee meeting

The following documents are made available to the Committee:

1. **Technical Briefing**

2. **Scope and matrix:**
   https://www.nice.org.uk/guidance/indevelopment/gid-ta10649/documents

3. **Company cost comparison summary** from UCB Pharma Ltd.
   3a. Company cost comparison summary
   3b. Addendum 1
   3c. Addendum 2

4. **Clarification letters**
   4a. NICE request to the company for clarification on their submission
   4b. Company response to NICE's request for clarification
   4c. Company response to clarification question A15

5. **Patient group, professional group and NHS organisation submission** from:
   5a. Psoriasis Association
   5b. Psoriasis and Psoriatic Arthritis Alliance
   5c. British Association of Dermatologists

6. **Evidence Review Group report (updated after factual accuracy check)** prepared by Southampton Health Technology Assessments Centre.

7. **Evidence Review Group report – factual accuracy check**

Please note that the full company submission, the appendices and company model will be available upon request.

NICE National Institute for Health and Care Excellence

Bimekizumab for treating moderate to severe plaque psoriasis

Technical briefing

This slide set is the technical briefing for this appraisal. It has been prepared by the technical team and 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 appraisal committee meeting and is expected reading for committee members. The submissions made by the company, consultees and nominated experts as well as the ERG report are available for committee members, and are optional reading.

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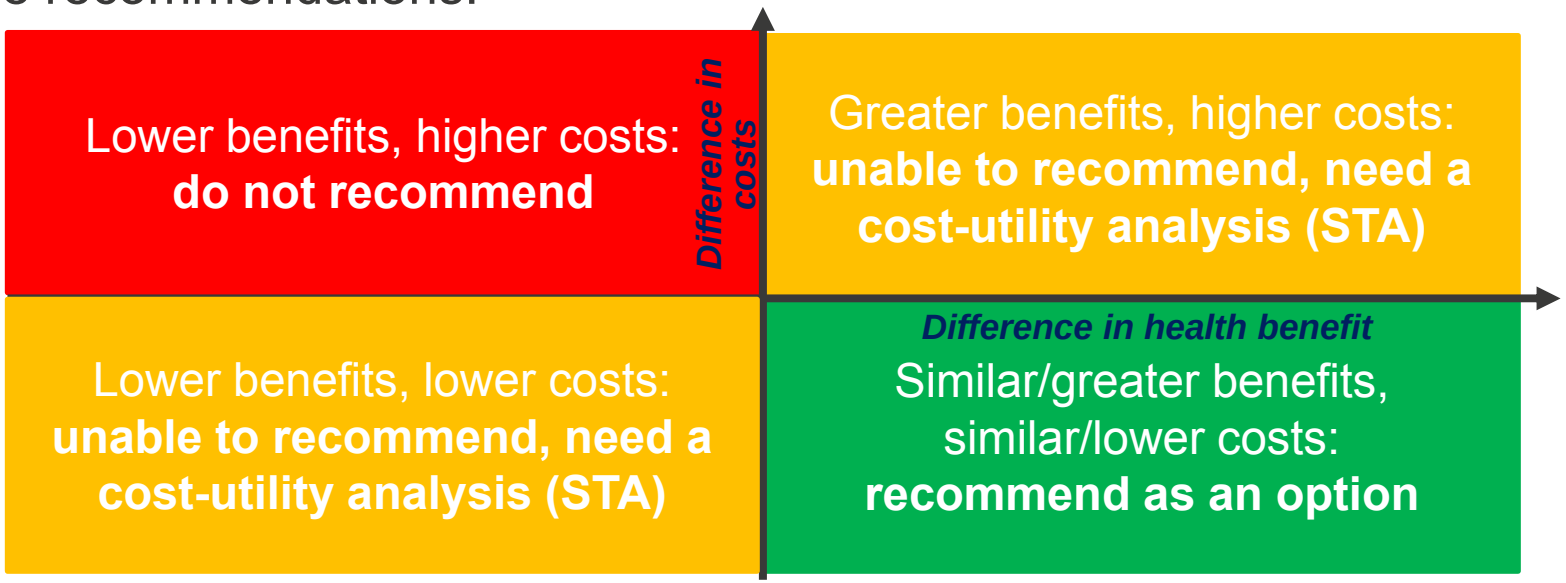
Fast Track Appraisals: Cost comparison

This topic is proposed as an FTA using cost comparison methods

- FTAs are appraisals in which less-detailed discussion is sufficient
  - Cost comparison FTA considered if the technology provides **similar/greater benefits** at **similar/lower cost** vs a **NICE-recommended** comparator

- Possible recommendations:



  - If a technology is recommended through cost comparison, guidance states:
    - ***"If patients and their clinicians consider both the technology and comparators to be suitable treatments, the least costly should be used"***

Key issues

Company has proposed this appraisal follows the FTA process based on bimekizumab having similar health benefits and costs to risankizumab (TA596), ixekizumab (TA442) and brodalumab (TA511).

- Are the company's chosen comparators (risankizumab, ixekizumab and brodalumab) relevant comparators?
- Are the health benefits and safety of bimekizumab and the company's chosen comparators similar?
- Are the costs of bimekizumab and the company's chosen comparators similar?
- Should the [redacted] be considered in the cost comparison? If yes, to what extent?
- Is it reasonable to recommend bimekizumab in the same way as risankizumab, ixekizumab and brodalumab ?

Abbreviations: FTA: fast track appraisal, TA: technology appraisal

Plaque psoriasis - disease background

- Chronic inflammatory condition characterised by flaky, scaly, itchy and red plaques on skin
- Varies in severity and distribution ranging from small patches on the elbows and knees to almost complete body coverage
- Unpredictable, relapsing and remitting course
- Associated with comorbidities such as depression, anxiety, arthritis, cardiovascular disease
- Graded as mild, moderate or severe (based on location, area affected, severity of lesions and impact on individual)
- Population:

NICE

Source: Bimekizumab NICE scope and company submission Section B.1.3.1

Measuring clinical effectiveness

Psoriasis Area and Severity Index (PASI): 0 to 72		
Assesses disease at 4 body regions, and measures 4 clinical signs (erythema, induration / papulation, excoriation and lichenification) on a scale of 0-4		
0 – 9	**10-19**	**≥20**
Mild to moderate	severe	Very severe
Response	• 75% reduction in the PASI score (PASI 75) from when treatment started or • 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started	

Dermatology Life Quality Index (DLQI): 0 to 30		
10-item questionnaire covering 6 domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment; 0(no impact) to 3 (worst impact)		
0 – 1	**6 – 10**	**11 – 20**
No effect	Moderate effect	Large effect
Response	≥5 point improvement considered a clinically important difference	

Investigator's Global Assessment (IGA): 0 to 4				
Clinician's impression of patient's psorasis based on severity of erythema, papulation / induration, oozing / crusting and lichenification				
0	**1**	**2**	**3**	**4**
Clear	Almost clear	Mild	Moderate	Severe

Definition of severity

Table 1. Definitions of psoriasis per different guidelines and nurse survey

Guidelines	Definitions of plaque psoriasis	PASI	DLQI
BAD[6]	Severe	≥10	>10
NICE[7]	Severe	≥10	>10
	Very severe	≥20	≥18
EMA[8]	Mild to moderate	<10	NA
	Moderate	≥10	NA
	Moderate to severe	10 to 20	NA
	Severe	>20	NA
European Consensus*[9]	Mild	≤10	≤10
	Moderate to severe	>10	>10

Psoriasis definitions based on nurse survey

Mild	Moderate	Severe
0–5	5–10	≥10

BAD: British Association of Dermatologists; BSA: body surface area; DLQI: Dermatology Life Quality of Index; EMA: European Medicines Agency; NICE: National Institute for Health and Care Excellence; PASI: Psoriasis Area Severity Index; *Experts from 19 European countries participated and defined items through a four-round Delphi process

NICE

NICE guidance

- Disease is severe defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more
- and a Dermatology Life Quality Index (DLQI) of more than 10

Patient and clinical perspective

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

Impact of psoriasis

psoriasis is a relapsing/remitting life-long disease with varying degree of severity; impact sleep, work ability and social interactions

not always visible to others, itch causes great distress to patients and should be considered as an outcome

People would like

Consideration of high-impact and difficult-to-treat sites such as palms, soles, flexures, genitals – do not produce a high PASI score

Consideration to people who have received all biological therapies and then had treatment failure: choice, accessibility and options

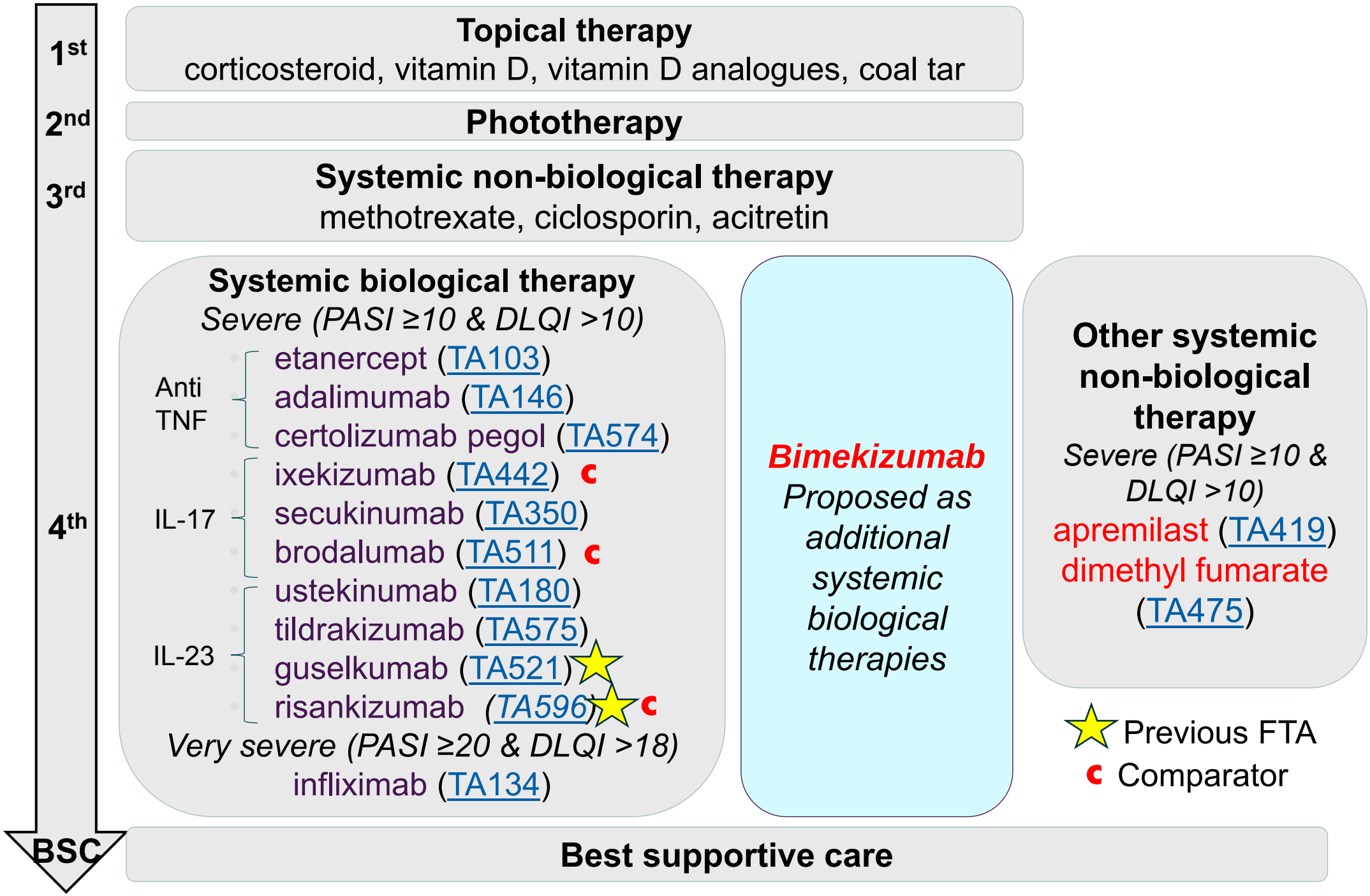
Bimekizumab

Dual specificity: humanised immunoglobulin monoclonal antibody that binds to both interleukin (IL)-17A and IL-17F to inhibit the IL-17 pathway

NICE

Source: British Association of Dermatologists [BAD], Psoriasis and Psoriatic Arthritis Alliance [PAPAA], Psoriasis Association.

Company's positioning of bimekizumab



Abbreviations: DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index TA: technology appraisal

New BAD guidelines (2020)

Previous version of BAD guidelines recommended ustekinumab, adalimumab and secukinumab for 1st line use, before other available biologics.

Recent 2020 guidelines update revised this recommendation, such that **all of currently licensed biologic therapies are now equally recommended as 1st or 2nd line** biologic options for adults with psoriasis who fulfil the criteria for biologic therapy. The choice of therapy should be tailored to each patient. The only specific recommendations regarding the choice of biologic are as follows:

- For people with coexisting **psoriatic arthritis**, **a TNF antagonist or an IL-17 antagonist*** should be offered as 1st line therapy.
- Of TNF antagonists, etanercept should be used when other available biologic agents have failed or cannot be used, or where a short half-life is important. Infliximab should be reserved for use in people with very severe disease, or where other available biologic agents have failed or cannot be used, or where weight-based dosing is a priority.

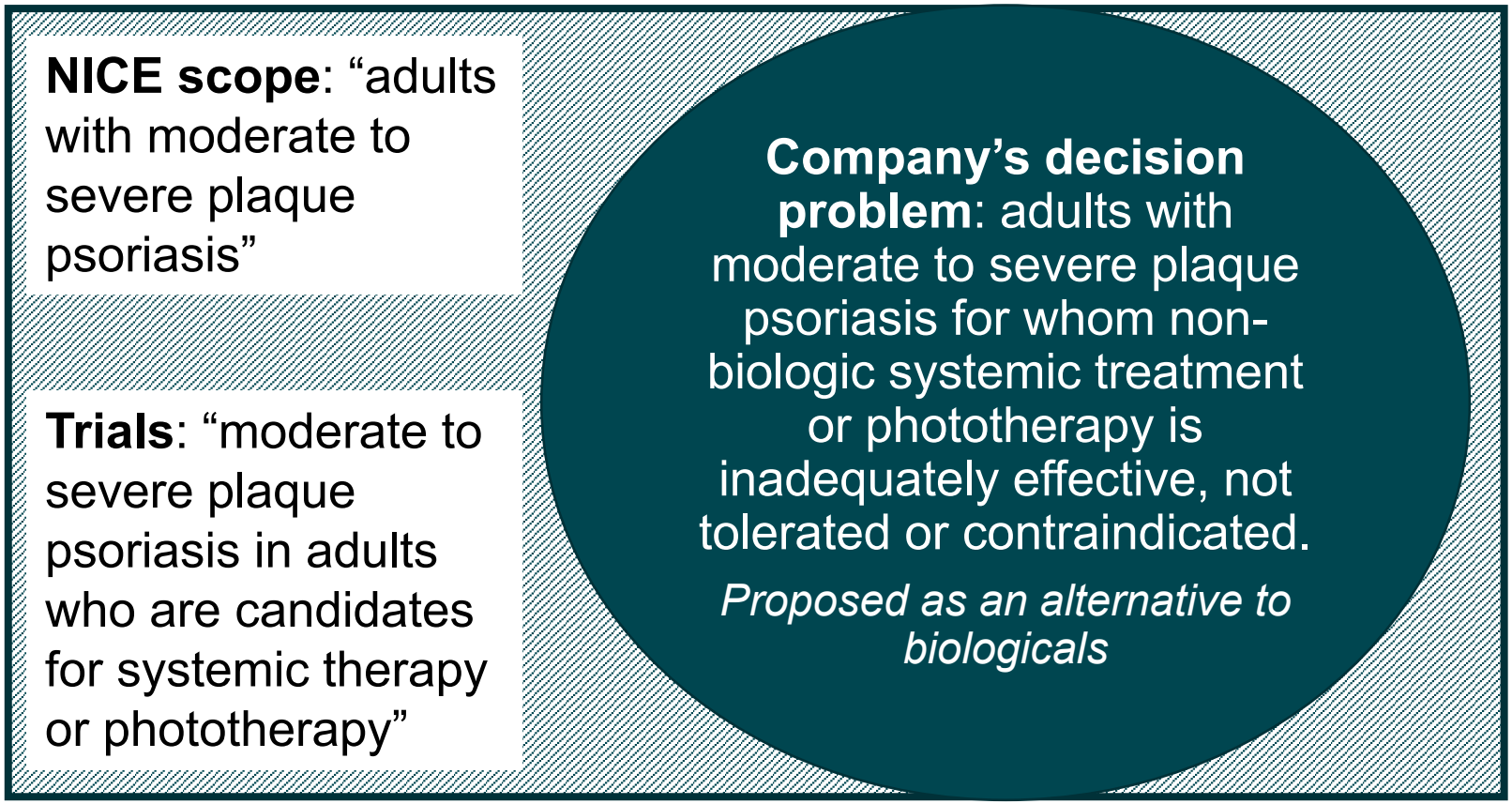
Footnotes: *brodalumab is not licensed for psoriatic arthritis
Abbreviations: BAD: British Association of Dermatologists, IL: interleukin; TNF: Tumor necrosis factor.

The technologies

	Bimekizumab	Risankizumab (TA596)	Ixekizumab (TA442)	Brodalumab (TA511)
Mode of action	Anti-IL-17A & IL-17F	Anti-IL-23	Anti-IL-17A	Anti-IL-17RA
Marketing authorisation	[redacted]	Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy		
Posology and method of administration	• [redacted] • [redacted]	• 150 mg (two 75 mg) administered by SC injection at weeks 0, 4 and every 12 weeks onwards • 'Consideration should be given to discontinuing treatment in patients who have shown no response after **16 weeks** of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.'	160 mg administered by SC injection at week 0, followed by 80 mg every 2 weeks until week 12. After week 12, 80 mg every 4 weeks.	210 mg administered by SC injection at weeks 0, 1 and 2, followed by 210 mg every 2 weeks.
Monitoring	Not available; company submission: the same as with other biologics	• Tuberculosis monitoring (pre-treatment evaluation and monitoring for active tuberculosis during and after treatment) • Monitoring of psoriasis response to treatment		

Abbreviations: IL: interleukin; RA: receptor A; SC: subcutaneous

Decision problem – population



- The population in the submission is narrower than the population in the scope.
- Bimekizumab trials are in line with previous NICE appraisals including guselkumab TA521 and risankizumab TA596.
- Marketing authorisation for bimekizumab is anticipated to be approved in July 2021
- Company expects a NICE recommendation for bimekizumab would similarly restrict its use to patients with severe disease (thus following NICE precedent).

Abbreviation: TA: technology appraisal

FTA choice of comparator (1)

	Risankizumab (FTA; TA596)	Ixekizumab (STA; TA442)	Brodalumab (STA; TA511)
Company rationale	• [redacted] • Most recently approved biologic (risankizumab) and 2 other IL-17-targeting treatments (ixekizumab and brodalumab) • Comparator choice validated by clinical experts at an advisory board as representing reasonable clinical comparators to bimekizumab • 2 previous cost-comparison FTAs in psoriasis (TA521, TA596) supports that a cost-comparison does not need to be conducted versus all biologics		
Recommendation	• PASI ≥10 & DLQI >10 in people not responsive to systemic therapy (severe disease)		
	Assessment at **16 weeks**. Treatment continued if PASI 75 OR PASI 50 and 5 point reduction in DLQI	Assessment at **12 weeks**. Treatment continued if PASI 75 OR PASI 50 and 5 point reduction in DLQI	
Cost comparator	**Guselkumab**	No cost-comparator – single technology appraisals	
Network meta-analysis	Comparable PASI response to guselkumab; better PASI response rates than other biologicals	More effective than adalimumab & ustekinumab; similar to infliximab & secukinumab	2nd most effective (after ixekizumab). Ranked consistently high in all sensitivity analyses.
Safety	Similar to other biologicals	Similar to other biologicals	Similar to other biologicals
Costs/ ICER	Costs similar/lower than guselkumab	Most plausible ICER likely in line vs other biologicals	ICERs dominate or <25,000 £/QALY vs other biologicals

NICE

Abbreviations: FTA: fast track appraisal, DLQI: Dermatology Life Quality Index; ICER: incremental cost effectiveness ratio; IL: interleukin; PASI: Psoriasis Area and Severity Index, QALY: quality-adjusted life year; STA: single technology appraisal; TA: technology appraisal

FTA choice of comparator (2)

- **ERG** considers the chosen cost-comparators adequately represent the NICE recommended treatments for plaque psoriasis as a whole:
  - bimekizumab is pharmacologically similar to the comparators
  - 3 highest ranking treatments on PASI 75 in company's NMA (after bimekizumab)
  - [redacted]
- Expert clinical advice to the ERG suggests that these 3 comparators would be expected to have a reasonable market share

- **Technical team** agrees that the chosen comparators likely adequately represent NICE recommended treatments as a whole in terms of effectiveness
- But uncertainty on whether they adequately represent costs, because of introduction of biosimilar adalimumab in 2019 (and etanercept in 2016)
  - All recent technology appraisal guidance in psoriasis state that "If patients and their clinicians consider [*a new drug*] to be one of a range of suitable treatments, the least expensive should be chosen (taking into account administration costs, dosage, price per dose and commercial arrangements)."
  - Therefore, if judged suitable, adalimumab or etanercept likely to be offered before bimekizumab

Abbreviations: DLQI: Dermatology Life Quality Index; NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index

FTA choice of comparator (3)

	Scrutiny assessment
Is the technology pharmacologically similar to the comparator(s)?	✓
Does the company's decision problem cover: a) all (decreasing risk) or only part (increasing risk) of the technology's marketing authorisation for this indication? b) all (decreasing risk) or only part (increasing risk) of the population for whom the comparator has been recommended by NICE?	a) Increasing risk, but in line with expected use b) Decreasing risk
Has the company made a comparison to a relevant NICE-recommended comparator?	✓
Are there any risks in making a case against this NICE-recommended comparator?	Biosimilar adalimumab products became available in 2019

NICE

"If patients and their clinicians consider both the technology and comparators to be suitable treatments, the least costly should be used"

Clinical effectiveness

FTA clinical effectiveness

	Scrutiny assessment
Has the company presented evidence using the same outcome measures as those used in the cost-effectiveness model for the NICE-recommended comparator?	
Does the technology have similar (or improved) efficacy to the comparator?	
Is the adverse event profile of the technology similar to that of the NICE-recommended comparator?	
Overall, is the treatment likely to offer similar or improved health benefits compared with the NICE-recommended comparator?	

Clinical effectiveness evidence

Comparator vs bimekizumab	Evidence	Trial name
Placebo	Direct trial	BE READY
Placebo and ustekinumab	Direct trial	BE VIVID
Adalimumab	Direct trial	BE SURE
Secukinumab	Direct trial	BE RADIANT
All other comparators (including risankizumab, brodalumab and ixekizumab)	Indirect evidence, Network meta analysis	-

Bimekizumab trials (1)

BE READY (vs placebo)	BE VIVID (vs placebo vs ustekinumab)
Design: 56-week, multi-centre, double-blind, patients randomised 4:1 to bimekizumab 320 mg Q4W or placebo for 16 weeks. Followed by a randomised-withdrawal period: at week 16, patients on bimekizumab with PASI 90 response were re-randomised 1:1:1 to bimekizumab 320 mg Q4W or Q8W or placebo. Patients without a response at week 16 or who relapsed* during the withdrawal phase were eligible to enter an open-label bimekizumab 320 mg Q4W 'escape' arm. Week 16 responders initially randomised to placebo remain on placebo after the initial treatment period.	**Design:** 52-week, multi-centre, double-blind, patients randomised 4:2:1 to receive bimekizumab 320 mg Q4W, ustekinumab 45/90 mg Q12W or placebo for 16 weeks Followed by 36-week maintenance period. At week 16, patients on placebo switched to receiving bimekizumab 320 mg Q4W.
Population: N=435	**Population**: N=567
Intervention: Bimekizumab 320mg	Intervention: Bimekizumab 320mg
Comparators: Placebo	**Comparators:** placebo and ustekinumab 45/90 mg
1º outcome: PASI90 and IGA0/1, at week 16	**1º outcome**: PASI90 and IGA0/1, at week 16
2º outcome: Other PASI responses including PASI75 and PASI100, IGA 0, safety	**2º outcome:** Other PASI responses including PASI75 and PASI100, IGA 0, safety

End of the maintenance period, patients could either enter into the open-label extension study (BE BRIGHT), if eligible, or move onto the safety follow-up.

NICE

Abbreviations: IGA0/1: investigator's global assessment response 0/1 response (represented by an IGA score of 'clear' (0) or 'almost clear' (1)) with at least a two-category improvement from baseline; PASI: Psoriasis Area and Severity Index; Q4W: every 4 weeks; Q8W: every 8 weeks

Bimekizumab trials (2)

BE SURE (vs adalimumab)	BE RADIANT (vs secukinumab)
Design: 56-week, multicentre, double-blind study, patients randomised 1:1:1 to receive bimekizumab 320 mg Q4W; bimekizumab 320 mg Q4W, switching to Q8W from Week 16; or adalimumab 40 mg every 2 weeks (Q2W), switching to bimekizumab 320 mg Q4W at Week 24.	**Design:** 48-week, multi-centre, double-blind, patients randomised 1:1 to receive bimekizumab 320 mg Q4W or secukinumab 300mg Q4W. At Week 16, patients were randomised 1:2 to receive bimekizumab 320 mg Q4W or Q8W. At the end of the 48-week double blind period, patients could enter a 96-week open label extension period.
Population: N=478	**Population**: N=743
Intervention: Bimekizumab 320mg	**Intervention:** Bimekizumab 320
Comparators: Adalimumab 40mg	**Comparators:** Secukinumab 300mg
1º outcome: PASI90 and IGA0/1, at week 16	**1º outcome**: PASI 100 at week 16
2º outcome: Other PASI responses including PASI75 and PASI100, IGA scores. Safety	**2º outcome:** Other PASI responses including PASI75 and PASI 100, safety

At the end of the maintenance period, patients could either enter into the open-label extension study (BE BRIGHT), if eligible, or move onto the safety follow-up.

NICE

Abbreviations: IGA0/1: investigator's global assessment response 0/1 response (represented by an IGA score of 'clear' (0) or 'almost clear' (1)) with at least a two-category improvement from baseline; Psoriasis Area and Severity Index; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks

Bimekizumab trials (3)

ERG

- Trials well designed with low risk of bias
- Patient populations representative of NHS
- Populations broadly comparable with the trial populations for the company's cost-comparators with respect to age, sex and disease duration; but the proportion of patients who had used prior biologic therapy varied more widely across the cost-comparator trials (7.9% to 46%) which may reflect changing practice over time.

Technical team

- Timepoint for assessment of response to induction therapy differs between bimekizumab and company's chosen comparators:
  - response to treatment with ixekizumab and brodalumab should be assessed at 12 weeks (TA511 and T442), while response to bimekizumab and risankizumab (TA596) should be assessed at 16 weeks.
- PASI 90 and PASI 100 responses are increasingly being recognised as important treatment goals for patients, aiming to achieve complete or near complete clearance of psoriasis (EuroGuiDerm guidelines, December 2020). The committee has previously acknowledged complete clearance of psoriasis symptoms is important to patients (TA521 and TA442). However, PASI 75 response is the main outcome used in economic modelling in current submission and all prior NICE guidance in psoriasis, as it is linked to definition of adequate response in NICE guidance*.

NICE

Footnote: *An adequate response is defined as:
- a 75% reduction in the PASI score (PASI 75) from when treatment started or
- a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started

Abbreviations: Psoriasis Area and Severity Index; TA: technology appraisal

Trial results: PASI 90 and PASI 100

- Across all trials, bimekizumab demonstrated **higher response rates** compared with placebo, ustekinumab, adalimumab [redacted] for both **PASI 90** (all p<0.001; [redacted]) and **PASI 100** (all p<0.001; p-value nominal for comparison with ustekinumab) at Week 16

[redacted]

Footnotes: *** p<0.001. PASI 90 response rate for BKZ versus SEC was not included in the BE RADIANT testing hierarchy and thus was not controlled for multiplicity, PASI 100 response rate for BKZ versus UST was not included in the BE VIVID testing hierarchy and thus was not controlled for multiplicity the p-value for this comparison is therefore a nominal p-value. For BE SURE, the BKZ Q4W and the BKZ Q4W/Q8W arms were combined for this analysis as all patients received BKZ Q4W through to week 16.

Abbreviations: ADA: adalimumab; BKZ; bimekizumab; PASI: Psoriasis area and severity index; PBO: placebo; Q4W: every 4 weeks; SEC: secukinumab; UST: ustekinumab.

Source: company submission figures 8 and 9 p. 66

Trial results: PASI 50, 75, 90 and 100

- [redacted] of patients on bimekizumab achieved a **PASI 75** response by Week 16
- Bimekizumab achieved **higher PASI 75** response rates vs placebo, [redacted] and adalimumab (all nominal p<0.001), and [redacted]
- No statistical analyses conducted for PASI 50 response rates

Outcome at week 16	BE READY		BE VIVID			BE SURE		BE RADIANT	
	PBO (n=86)	BKZ Q4W (n=349)	PBO (n=83)	BKZ Q4W (n=321)	UST (n=163)	BKZ Q4W (n=319)	ADA (n=159)	BKZ Q4W (n=373)	SEC (n=370)
PASI 50 n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75 n (%)	2 (2.3)	333 (95.4)	[redacted]	[redacted]	[redacted]	295 (92.5)	110 (69.2)	[redacted]	[redacted]
PASI 90 n (%)	1 (1.2)	317 (90.8)	4 (4.8)	273 (85.0)	81 (49.7)	275 (86.2)	75 (47.2)	[redacted]	[redacted]
PASI 100 n (%)	1 (1.2)	238 (68.2)	0	188 (58.6)	34 (20.9)	194 (60.8)	38 (23.9)	[redacted]	[redacted]

Footnotes: PASI 50 data at Week 16 for BE RADIANT is from a post-hoc analysis conducted for the sake of completeness of this table. PASI 50 response rates were not part of the protocol for this trial.

Abbreviations: ADA, adalimumab; BKZ, bimekizumab; IGA, Investigator's Global Assessment; NRI: non-responder imputation; PASI, Psoriasis Area and Severity Index; PBO, placebo; RS: randomised set; SEC, secukinumab; UST, ustekinumab.

Source: company submission table 17 p.67

Trial results: IGA 0/1

- At Week 16, bimekizumab achieved significantly higher response rates for IGA 0/1 vs placebo, ustekinumab and adalimumab (all p<0.001) [redacted].
- IGA 0 response rate at Week 16 was [redacted]

Abbreviations: IGA 0/1 response was defined as a score of 'clear' or 'almost clear' with at least a 2-category improvement from baseline, and IGA 0 was defined as a score of 'clear' with at least a 2-category improvement from baseline.

Trial results: DLQI 0/1

- At Week 16, a high proportion of patients had a DLQI score of 0 or 1, indicating 'no impact on patient's life', which was [redacted]

*** p<0.001.

Footnotes: DLQI 0/1 response rate was not included in the testing hierarchy for any of the trials and thus comparisons were not controlled for multiplicity, all p-values are therefore nominal p-values.

Abbreviations: BKZ, bimekizumab; CSR: clinical study report; DLQI, Dermatology Life Quality Index; NRI: non-responder imputation; PBO, placebo; RS: randomised set.

Source: company submission figure 11 p. 71

Safety profile

- Bimekizumab safety data were pooled to increase sample size
  - Bimekizumab has a comparable safety profile with anti-IL-17A biologics
  - Bimekizumab associated with a higher rate of oral candidiasis infections compared to placebo (due to IL-17 pathway role in defence against candida species) and compared to other anti-IL-17 class biologics. But the majority ([redacted]) of cases of oral candidiasis were mild to moderate and were easily managed with standard anti-fungal therapy and did not lead to treatment discontinuation

ERG

- The trial data do not suggest any notable safety concerns for bimekizumab vs active comparators

Abbreviations: AE: adverse event

Company's network meta-analysis (NMA)

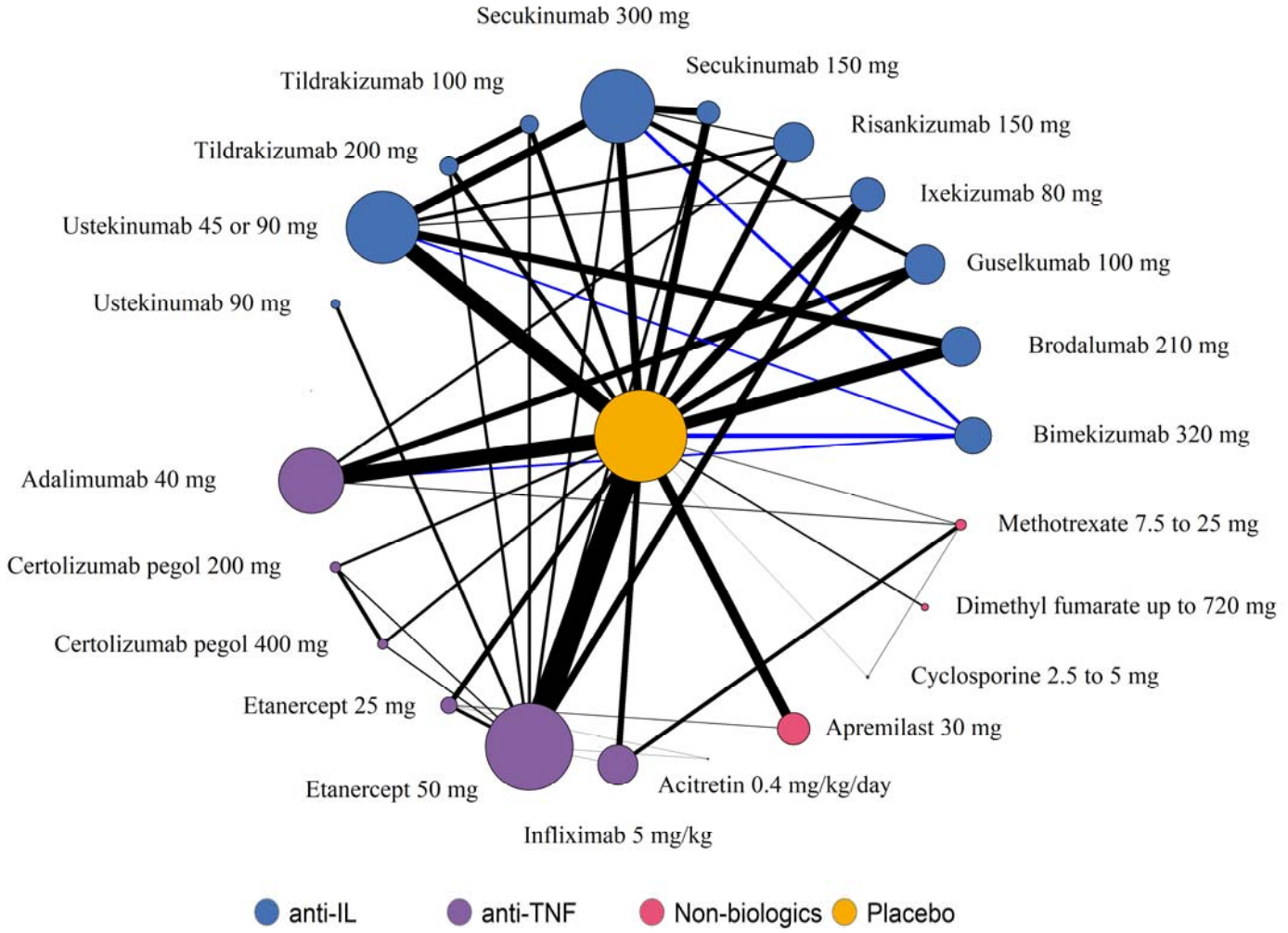
- Included following outcomes:
  - PASI (PASI 50, 75, 90, 100),
  - safety (AEs, SAEs, discontinuation due to AEs)
- Timepoints: 10-16 weeks
- 84 trials included in the network
- Fixed and random effect models were compared
- The random effects model that allowed for relaxation of the proportional treatment effects assumption was considered the most appropriate
  - Relaxation of the proportional treatment effect (not featured in previous appraisals): ranking of treatments in probability of PASI response is not necessarily the same across each of the 4 PASI-response categories

- ERG considers that NMA's approach is appropriate although company did not include DLQI (included in previous appraisals: TA521 guselkumab; TA596 risankizumab)
- ERG considers the company's justification for the random effect model reasonable
- NMA inclusion criteria are broader than decision problem and include trials of systemic non-biologic treatments (results are not presented). ERG assumes aim is to strengthen connections within the network. It could boost statistical power but increase heterogeneity. ERG does not consider that this biases in favour of bimekizumab

NICE

Abbreviations: AEs: adverse events; DLQI: Dermatology Life Quality Index; NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index; SAEs: Serious adverse events.

Company's network meta-analysis (NMA)



Abbreviations: IL: interleukin; NMA: network meta-analysis; SLR: systematic literature review; TNF: tumour necrosis factor.
Source: company submission, figure 16 p.84

Company NMA results for efficacy

- [redacted]
- [redacted]

Forest plot of probabilities of achieving at least given PASI response at 10–16 weeks

[redacted]

Source: company submission figure 17 p. 87. **Abbreviations:** NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index

Company NMA result for safety

[redacted]

[redacted]

ERG has no particular concerns around comparative safety

NICE

Note: unclear if all studies included in NMA used the same definition of serious adverse events.
Source: company submission appendices, Appendix D.1.1.16.2, tables 20-28.

Network meta analysis conclusions

ERG

- Can assume the claim of similar or greater efficacy and safety between bimekizumab versus other biologics is acceptable, based on robust results of the company's NMA, and the consistency of these results with those from previous NICE appraisals.

Technical team

- Company's NMA is line with the NMA by the Cochrane Skin Group (Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis).
  - Included 140 studies for 19 systemic medicines, published until January 2019 (living review)
  - NMA showed that clinical effectiveness of infliximab, ixekizumab, risankizumab, bimekizumab, guselkumab, secukinumab and brodalumab was similar for PASI 75 and PASI90. The main limitation was the limited number of studies included for bimekizumab.
  - For the risk of serious side effects, there were no significant differences between any of the systemic medicines compared with placebo treatment. However, the number of serious side effects was very low, and the rankings were based on low- to very low- or moderate-certainty evidence, so they should be interpreted with caution.

FTA clinical effectiveness

	Scrutiny assessment
Has the company presented evidence using the same outcome measures as those used in the cost-effectiveness model for the NICE-recommended comparator?	✓
Does the technology have similar (or improved) efficacy to the comparator?	✓
Is the adverse event profile of the technology similar to that of the NICE-recommended comparator?	✓
Overall, is the treatment likely to offer similar or improved health benefits compared with the NICE-recommended comparator?	✓

Cost comparison

Company cost-comparison model

Resource use assumptions

- Healthcare resource costs assumed to be similar to risankizumab, ixekizumab and brodalumab and excluded from the cost comparison
  - Similar monitoring
  - Comparable safety profile
  - Similar treatment administration
  - Similar cost of subsequent therapies
- **Therefore company model considers only acquisition costs**

ERG

- Approach is appropriate and consistent with previous cost-comparisons (risankizumab TA596 & guselkumab TA521)

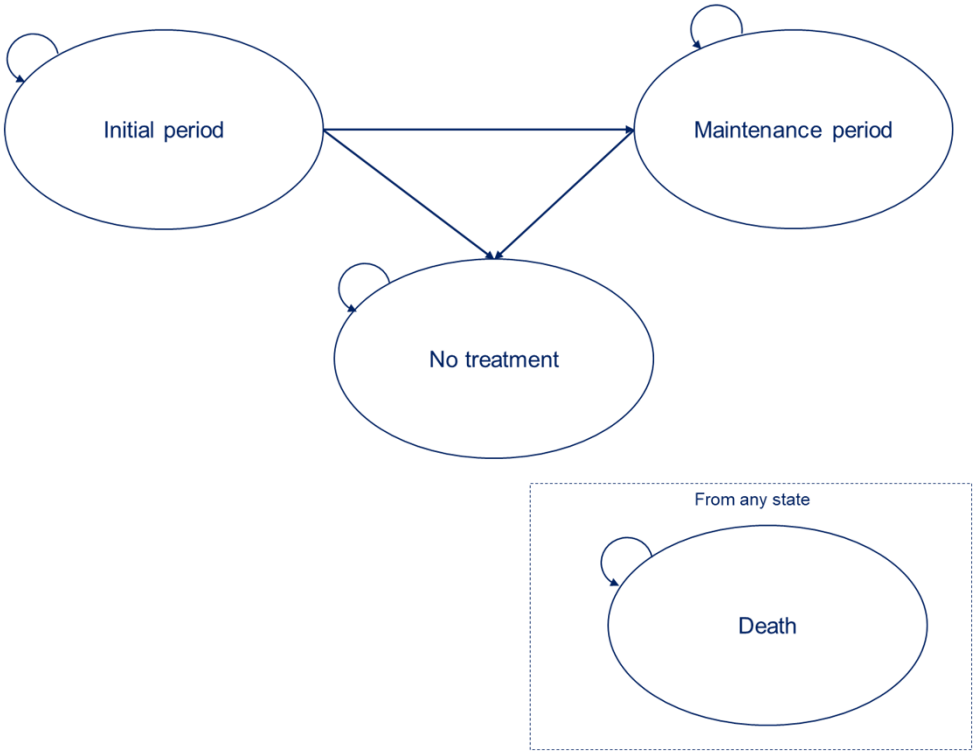
Technical team: Subsequent treatments after non-response would start 4 weeks earlier with ixekizumab and brodalumab (assessment after 12 weeks; TA442, TA511) than with bimekizumab and risankizumab (assessment after 16 weeks; TA596). However, the impact of this 4-week difference on total costs is likely negligible, considering only a small proportion of patients* stop treatment after the induction period and in the context of the long model horizon.

*[redacted]; PASI 75 non-response in company's network meta-analysis

Company cost-comparison model

Model approach & assumptions

- Costs are estimated over 10-year time horizon
- Model includes a 12 to 16-week induction phase, aligned with each therapy licence
- PASI 75 response after induction phase: patients go on to a maintenance phase
- No response: patients stop treatment and incur no further costs
- PASI 75 response rate based on company's NMA; equal efficacy assumed: [redacted]
- On maintenance: equal probability of long term discontinuation (20% per year in base case)



ERG: approach is appropriate and consistent with previous cost-comparisons (risankizumab TA596 & guselkumab TA521) and cost-effectiveness analyses for ixekizumab TA442 & brodalumab TA511

Technical team: there is a potential impact of treatment adherence on discontinuation of maintenance therapy. But unlikely sufficient evidence to assess impact of dosing frequency on adherence. 20% discontinuation rate is consistent with previous cost-comparisons in psoriasis.

FTA clinical effectiveness (1)

	Scrutiny assessment
Is the acquisition cost of the technology similar to/lower than the comparator (including patient access schemes/other discounts)?	✘ But it has since been reduced
Are the healthcare resource costs associated with the technology likely to be similar to/lower than the respective costs for the NICE recommended comparator?	✓ Costs will be similar
Is the technology likely to affect the downstream costs of managing the condition and has this been accounted for?	✓ Costs will be similar
Are the overall costs for the technology similar to/lower than the comparator?	✘ But it has since been reduced

Company submission: cost comparison with PAS for bimekizumab and comparator (deterministic)

Bimekizumab [redacted]

Therapy (dose)	Induction		Maintenance (doses per year)	List price per dose	PAS price per dose	Total costs over 10 years (£)	Difference over 10 years (£)
	Duration	Doses					
Bimekizumab (2 x 160 mg)	16 weeks	5	6.5	[redacted]	[redacted]	[redacted]	
Brodalumab (1 x 210 mg)	12 weeks	8	26.0	£640	[redacted]	[redacted]	[redacted]
Ixekizumab (1 x 80 mg)	12 weeks	8	13.0	£1,125	[redacted]	[redacted]	[redacted]
Risankizumab (2 x 75 mg)	16 weeks	3	4.3	£3,326	[redacted]	[redacted]	[redacted]

Abbreviation: PAS: patient access scheme

Source: ERG addendum 2 table 1 p. 2

Other ERG scenario and sensitivity analyses

Discontinuation rate affects cost comparison with brodalumab

Scenario (all deterministic)		Cost difference over 10 years: bimekizumab minus comparator		
		Brodalumab	Ixekizumab	Risankizumab
Base case		[redacted]	[redacted]	[redacted]
PASI 75 response (base case [redacted])	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted] (lower CrI)[a]	[redacted]	[redacted]	[redacted]
	[redacted] (upper CrI)[a]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon (base case 10 years)	5 years	[redacted]	[redacted]	[redacted]
	20 years	[redacted]	[redacted]	[redacted]
Discount rate (0%)	3.5% per year	[redacted]	[redacted]	[redacted]
Mortality (base case general population)	Exclude mortality	[redacted]	[redacted]	[redacted]
	Multiplier 1.42 (TA511)	[redacted]	[redacted]	[redacted]
Discontinuation (base case 20%)	11% (Warren 2015)	[redacted]	[redacted]	[redacted]
	16% (-20%)[b]	[redacted]	[redacted]	[redacted]
	18.7% (TA511)	[redacted]	[redacted]	[redacted]
	19% (Egeberg 2018)	[redacted]	[redacted]	[redacted]
	24% (+20%) [b]	[redacted]	[redacted]	[redacted]
[redacted]				

[a] 95% CrI for bimekizumab from the company's indirect comparison; [b] Company's sensitivity analysis range +/- 20% of base case value
Abbreviations: CrI: credible interval; PASI: Psoriasis Area and Severity Index, TA: technology appraisal. **Source:** ERG addendum 2 table 2.

ERG scenario analyses (1)

[redacted] *has highest impact on cost-comparison*

- ERG:
  [redacted]
- The company
  [redacted]
- ERG clinical expert
  [redacted]
- ERG explore the impact of this [redacted] in an exploratory scenario analyses:
  - [redacted]
  - [redacted]
- On 8th June 2020, the company clarified that
  [redacted]

Abbreviations: PASI: Psoriasis Area and Severity Index, TA: technology appraisal

ERG scenario analyses (2)

[redacted] *has highest impact on cost-comparison results*

Scenario (deterministic)	Cost difference over 10 years: bimekizumab minus comparator		
	Brodalumab	Ixekizumab	Risankizumab
Base case	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

The company clarified that [redacted]

Technical team:

[redacted]

Abbreviations: PASI: Psoriasis Area and Severity Index, TA: technology appraisal; **Source:** ERG addendum 2 table 2.

[redacted]

Scenario (deterministic)	[redacted]	Cost difference over 10 years: bimekizumab minus comparator		
		Brodalumab	Ixekizumab	Risankizumab
Base case	[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]

Source: NICE technical team calculations

Innovation

Consultee comments:

- **British Association of Dermatologists**: targeting both IL-17A and IL-17F cytokines is a new treatment approach for psoriasis. Prior IL17 inhibitors only block IL-17A but IL17F also has an important role in the immunopathogenesis of psoriasis.
- **Psoriasis and Psoriatic Arthritis Alliance:** adding alternative treatment option to existing treatments and providing a different target if similar class therapies fail
- **Psoriasis association**: The dosing regime is particularly advantageous to patients – an injection once every 8 weeks allows greater freedom to get on with one's life especially when scheduling other healthcare requirements.

Equality

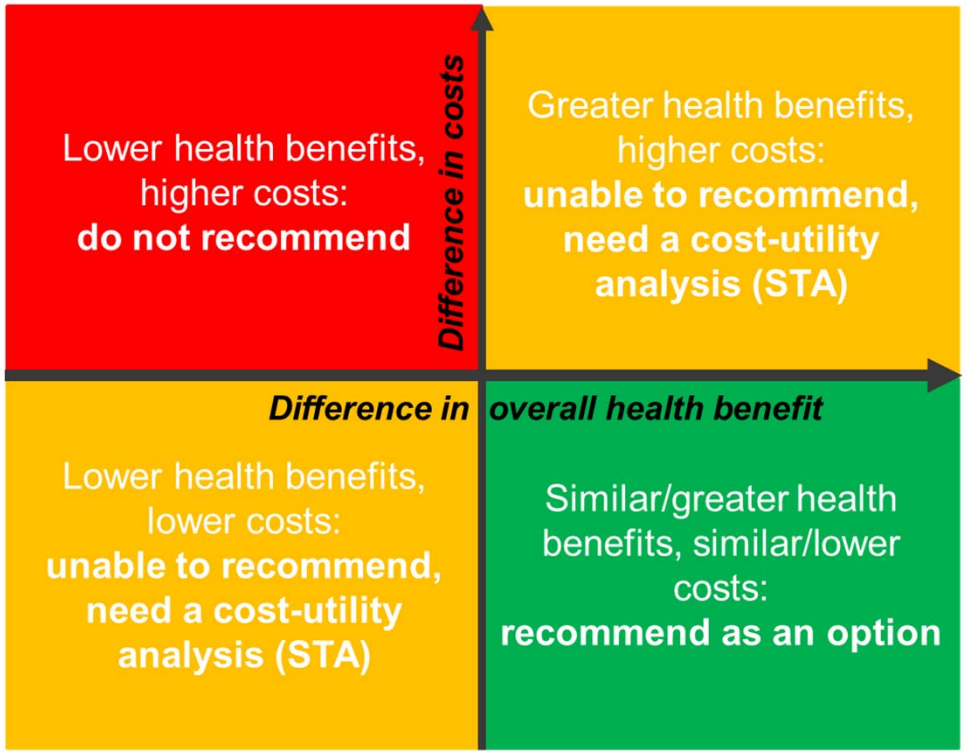
Consultee comments:

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

NICE

Sources: British Association of Dermatologists [BAD], Psoriasis and Psoriatic Arthritis Alliance [PAPAA], Psoriasis Association.

Potential recommendations: cost comparison



What is the committee view on:

- the choice of comparators
  - Specifically the exclusion of adalimumab
- the similarity of health benefits and safety of bimekizumab and comparators
- the similarity of costs of bimekizumab and comparators
- [redacted] during maintenance for the cost calculation
- is it reasonable to recommend bimekizumab in the same way as ixekizumab, risankizumab and brodalumab?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

ID2692 Bimekizumab for the treatment of moderate to severe plaque psoriasis

Document A

Company evidence submission summary for committee

UCB Pharma Ltd 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.

January 2021

File name	Version	Contains confidential information	Date
ID2692_Bimekizumab for psoriasis_UCB Pharma_Document A_12.01.21_ACIC REDACTED	**V1**	**Yes**	**January 2021**

Contents

Tables

Figures

A.1 The technology

The bimekizumab antibody was discovered in the UK and engineered for dual specificity using novel technology invented in the UK. Bimekizumab is a monoclonal antibody that is designed to selectively inhibit both the interleukin (IL)-17A and IL-17F cytokines.[1] Bimekizumab is anticipated to be licensed [redacted].

The BE VIVID, BE SURE and BE RADIANT active comparator-controlled trials, as well as results from a network meta-analysis (NMA), together provide direct and indirect evidence of statistically significantly higher PASI 90 and 100 response rates at Week 16 for bimekizumab versus all other treatments licensed for the treatment of plaque psoriasis (see Document B, Section B.3). From the first dose, bimekizumab has been shown to demonstrate both a rapid onset of response and superior efficacy compared with ustekinumab,[2] adalimumab[3] and secukinumab.[4] Bimekizumab demonstrates consistent achievement of response, with the majority of patients achieving complete skin clearance by Week 16 across the clinical studies. The rapid and high level of complete skin clearance, which extends to high-impact areas such as nails, scalp, palms and soles, is maintained over time with the 8-week dosing regimen. Long-term, durable skin clearance is supported by substantial improvements in quality of life (QoL) with most patients' daily lives no longer impacted by their psoriasis.

An overview of bimekizumab is presented in Table 1.

Table 1: Technology being appraised – B.1.2 (pages 13–14)

UK approved name and brand name	Approved name: bimekizumab Brand name: not available at the time of submission
Mechanism of action	Bimekizumab is a humanised immunoglobulin monoclonal antibody that binds to both IL-17A and IL-17F cytokines to inhibit the IL-17 pathway; this pathway is a pivotal driver of inflammation in psoriasis.[1, 5] If recommended, bimekizumab would be the only available treatment with this dual selective inhibition of IL-17A and IL-17F. While IL-17A is more potent and has been well-characterised as it is the target of existing treatments, IL-17F is ~30 times more abundant in skin lesions and can drive inflammation independently of IL-17A.[6, 7] Bimekizumab prevents these cytokines from binding to their cellular targets, inhibiting them from promoting inflammation, and thus reducing the symptoms of psoriasis. Selective inhibition of both IL-17F and IL-17A is a more effective approach than targeting IL-17A alone, resulting in unprecedented levels of complete skin clearance as demonstrated by the clinical evidence presented in this submission (Section B.3).[2-4, 8]
Marketing authorisation/CE mark status	European marketing authorisation is anticipated in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Bimekizumab is anticipated to be indicated for [redacted]
Method of administration and dosage	[redacted]

	[redacted]
Additional tests or investigations	Bimekizumab 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	[redacted] Cost of 16-week initial period (5 doses): [redacted] Cost of a full year of maintenance therapy (6.5 doses): [redacted]
Patient access scheme (if applicable)	[redacted]

Abbreviations: IL: interleukin; NHS: National Health Service; SmPC: summary of product characteristics.
Source: Draft SmPC for bimekizumab, see Appendix C.1.

A.2 Clinical pathway of care

The NICE clinical guidelines for psoriasis outline three potential stages of treatment for psoriasis.[9] Topical therapy as first-line treatment, phototherapy and systemic non-biological therapy as second-line treatments, and systemic biological therapies and other non-biological agents as third-line treatments.

It is proposed that bimekizumab be appraised as a treatment option in adult patients with plaque psoriasis, if:

- The disease is severe, as defined by a total PASI ≥10 and a DLQI >10 and
- The disease has not responded to other systemic treatments, including ciclosporin, methotrexate and phototherapy, or these options are contraindicated or not tolerated.

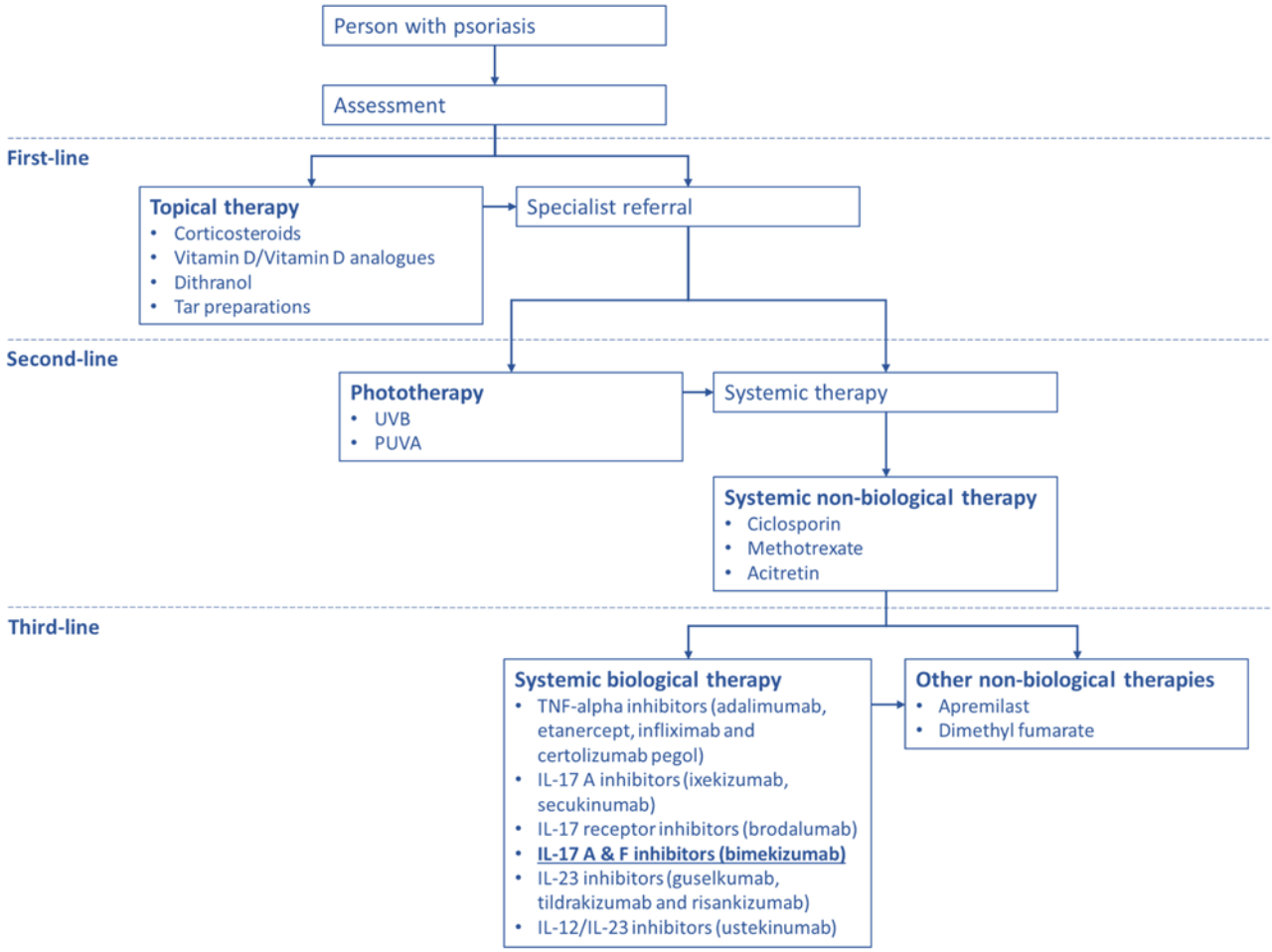
This positioning for bimekizumab is aligned with the expected use of a new biologic in clinical practice, and with all previous NICE recommendations for biologics in psoriasis (Figure 1).

The NICE guidance also recommends treatment discontinuation at the end of an initial treatment period (the length of which varies across treatments), if an 'adequate' response is not achieved, defined as:

- a 75% reduction in the PASI score (PASI 75) from when treatment started or
- a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.

Whilst PASI 75 represents an adequate response and has historically been used as a standard primary endpoint in many trials of psoriasis treatments, trials are now moving towards endpoints of PASI 90 or PASI 100.[10, 11] This reflects a shift in patient's treatment goals beyond achievement of simply an adequate response, and towards a more desirable response of complete or near complete skin clearance that can support towards patients being able to carry out their everyday lives without the burden of skin disease.[12, 13]

Figure 1: Clinical pathway for plaque psoriasis showing the proposed positioning of bimekizumab – B.1.3.1 (page 21)



Abbreviations: DMF: dimethyl fumarate; IL: interleukin; NICE: National Institute for Health and Care Excellence; PUVA: psoralen plus ultraviolet A; TNF: tumour necrosis factor; UVB: ultraviolet B.
Source: Adapted from the NICE pathway for psoriasis.[14]

A.3 Equality considerations

There are two relevant equality considerations that have been discussed in previous technology appraisals regarding biologics:

- PASI measurements may underestimate severity of disease for people with darker skin, such as skin types V and VI on the Fitzpatrick scale.[9]
- The DLQI may underestimate the impact of disease in certain groups, such as individuals who are older, socially isolated, not sexually active, suffering from anxiety or depression or those who are less able to complete the questionnaire due to sensory or learning disabilities.[9, 15]

A.4 Key drivers of the cost effectiveness of the comparator(s)

A.4.1 Clinical outcomes and measures

To date, eleven NICE technology appraisals have been published on biologics for the treatment of psoriasis in adult patients. Table 2 provides a summary of the key clinical assumptions from these appraisals and the preferred assumptions from the committee.

Table 2: Summary of key clinical assumptions in NICE appraisals of biologics in psoriasis – B.2.1 (pages 26–29)

Appraisal	Framework for economic analysis	Assumptions used in modelling	Committee's preferred assumptions and any uncertainties
Etanercept **TA103, 2006** **Anti-TNF**	Cost-utility analysis	• PASI 50 response required to continue receiving treatment	• The committee preferred a higher threshold of a PASI 75 response or a PASI 50 response with at least a 5-point reduction in DLQI
		• 20% annual discontinuation rate	• No comment from the committee
		• AEs not modelled	• The committee did not directly comment on the modelling of AEs • However, the committee stated that there was limited data available on AEs, and recommended that the BADBIR should be rapidly established to monitor AEs
Infliximab **TA134, 2008** **Anti-TNF**	Cost-utility analysis	• PASI 75 response required to continue receiving treatment	• The committee agreed that it was appropriate for treatment to be continued only in patients achieving a PASI 75 response • However, the committee ultimately aligned with the response definition approved for etanercept – a PASI 75 response or a PASI 50 response with at least a 5-point reduction in DLQI
		• 20% annual discontinuation rate	• The committee concluded that there was uncertainty around the annual discontinuation rate, and the true value was likely to lie between 20% and the ERG's estimate of 50% • Ultimately the committee accepted that the values adopted by the manufacturer were appropriate
		• AEs not modelled	• No comment from the committee
Adalimumab **TA146, 2008** **Anti-TNF**	Cost-utility analysis	• PASI 75 response required to continue receiving treatment • PASI 50 response for continuing treatment explored in sensitivity	• The committee did not directly comment on the appropriateness of using PASI 75 for the modelling of treatment continuation • However, the ultimate recommendation was for continuation of treatment in patients achieving a PASI 75 or a PASI 50

		analysis	response with at least a 5-point reduction in DLQI
		• 20% annual discontinuation rate	• No comment from the committee
		• AEs not modelled	• No comment from the committee
Ustekinumab **TA180, 2009** **Anti-IL-12/23**	Cost-utility analysis	• PASI 75 response required to continue receiving treatment	• The committee did not directly comment on the appropriateness of using PASI 75 for the modelling of treatment continuation • However, the ultimate recommendation was for continuation of treatment in patients achieving a PASI 75 response or a PASI 50 response with at least a 5-point reduction in DLQI
		• 20% annual discontinuation rate	• The committee heard from clinical experts that this estimate was reasonable
		• AEs not modelled	• No comment from the committee
Secukinumab **TA350, 2015** **Anti-IL-17A**	Cost-utility analysis	• PASI 75 response required to continue receiving treatment • PASI 50 response for continuing treatment explored in a scenario analysis	• The committee did not directly comment on the appropriateness of using PASI 75 for the modelling of treatment continuation • However, the committee stated that the recommendation for treatment continuation should be consistent with previous appraisals – a PASI 75 response or a PASI 50 response with at least a 5-point reduction in DLQI
		• 11.7% discontinuation at the end of the first year based on the FIXTURE and ERASURE trials • 20% annual discontinuation rate after the first year	• The committee concluded that 20% annual discontinuation may be an overestimate, but as this affected all biological treatments equally, this was likely to have a minimal effect
		• Costs and resource use associated with AEs were included in the model	• No comment from the committee
Ixekizumab **TA442, 2017** **Anti-IL-17A**	Cost-utility analysis	• PASI 75 response required to continue receiving treatment • PASI 50 response for continuing treatment explored in a scenario analysis	• The committee noted that the cost-effectiveness of ixekizumab increased when a PASI 50 stopping rule was applied, and that for patients with limited psoriasis on high impact areas (the hands and feet) a clinical improvement may not be appropriately accounted for by the PASI score • The committee therefore concluded that, in line with previous appraisals, treatment should be continued in patients achieving a PASI 75 or a PASI 50 response with at least a 5-point reduction in DLQI

		• 20% annual discontinuation rate	• No comment from the committee
		• AEs not modelled in the base case • Costs and resource use associated with AEs were explored in a scenario analysis	• The committee heard from clinical experts that the side effect profiles of biologics are generally similar, and it was therefore acceptable to exclude the disutility associated with adverse events from the modelling • However, the committee concluded that the company should have included the costs of adverse events in the model base case
Brodalumab **TA511, 2018** **Anti-IL-17RA**	Cost-utility analysis	• PASI 75 response required to continue receiving treatment	• The committee did not directly comment on the appropriateness of using PASI 75 for the modelling of treatment continuation • However, the ultimate recommendation was for continuation of treatment in patients achieving a PASI 75 response or a PASI 50 response with at least a 5-point reduction in DLQI
		• 18.7% annual discontinuation rate	• The committee preferred the company to use treatment-specific discontinuation rates, but understood that there were not enough data • The committee ultimately agreed that the assumption was acceptable for decision-making
		• Impact of serious infections on costs and HRQoL included in the base case • Impact of other AEs on costs and HRQoL explored in a scenario analysis	• No comment from the committee
Guselkumab **TA521, 2018** **Anti-IL-23**	Cost-comparison	• PASI 75 response required to continue receiving treatment	• The committee acknowledged that PASI 75 is a key outcome for informing treatment continuation after induction • However, the ultimate recommendation was for continuation of treatment in patients achieving a PASI 75 response or a PASI 50 response with at least a 5-point reduction in DLQI
		• 20% annual discontinuation rate	• No comment from the committee
		• AEs not modelled	• No comment from the committee
Certolizumab pegol **TA574, 2019** **Anti-TNF**	Cost-utility analysis	• PASI 75 response required to continue receiving treatment • PASI 50 response for continuing treatment explored in a scenario analysis	• The committee did not directly comment on the appropriateness of using PASI 75 for the modelling of treatment continuation • However, the ultimate recommendation was for continuation of treatment in patients achieving a PASI 75 response or a PASI 50 response with at least a 5-point reduction in DLQI

		• 20% annual discontinuation rate • Treatment-specific annual discontinuation explored in a scenario analysis	• The committee was aware that there was limited evidence to support a 20% annual discontinuation rate, but that this was consistent with previous appraisals so was acceptable for decision-making • The committee did not comment on the scenario analysis
		• AEs not modelled	• No comment from the committee
Tildrakizumab **TA575, 2019** **Anti-IL-23**	Cost-utility analysis	• PASI 75 response required to continue receiving treatment	• The committee did not directly comment on the appropriateness of using PASI 75 for the modelling of treatment continuation • However, the ultimate recommendation was for continuation of treatment in patients achieving at least a PASI 50 response at 12 weeks, and a PASI 75 response or a PASI 50 response with at least a 5-point reduction in DLQI at 28 weeks
		• 18.7% annual discontinuation rate	• No comment from the committee
		• AEs not modelled	• No comment from the committee
Risankizumab **TA596, 2019** **Anti-IL-23**	Cost-comparison	• PASI 75 response required to continue receiving treatment • PASI 50, PASI 90 and PASI 100 response for continuing treatment explored in scenario analyses	• The committee acknowledged that PASI 75 is a key outcome when deciding to continue treatment and appreciated that the company analyses also covered a range of outcomes • The ultimate recommendation was for continuation of treatment in patients achieving a PASI 75 response or a PASI 50 response with at least a 5-point reduction in DLQI
		• 20% annual discontinuation rate • 11%, 18.7% and 19% annual discontinuation rate explored in scenario analyses	• No comment from the committee
		• AEs not modelled	• No comment from the committee

Footnotes: Biologics are listed in the order in which they received NICE recommendation
Abbreviations: BADBIR: British Association of Dermatologists Biologics and Immunomodulators Register; DLQI: Dermatology Life Quality Index; ERG: Evidence Review Group; FAD: final appraisal determination; IL: interleukin; HRQOL: health-related quality of life; NICE: National Institute for Health and Care Excellence; PASI: Psoriasis Area Severity Index; RA: receptor antagonist; TA: technology appraisal; TNF: tumour necrosis factor.
Source: NICE FADs for biologic therapies approved for the treatment of moderate to severe psoriasis.[16-26]

A.4.2 Resource use assumptions

Resource use categories included in previous NICE technology appraisals of biologics for the treatment of adult patients with psoriasis include:

- Drug acquisition costs
- Drug administration costs
- Treatment monitoring costs
- Best supportive care/non-responder costs
- Adverse event costs

However, in line with the two previous cost-comparison fast-track appraisals (FTAs) in psoriasis (TA521 and TA596), the majority of these costs are considered to be equivalent across different biologics.[27, 28] The only costs considered in these cost-comparison models were drug acquisition costs, and these models were accepted by the respective committees for each appraisal.[25, 29] Thus, the same approach was taken in the current analysis.

A.5 Decision problem and NICE reference case

A.5.1 Population

The marketing authorisation for bimekizumab is expected to be for [redacted].

The submission focuses on a specific population within bimekizumab's marketing authorisation, considering bimekizumab as an alternative to other biologic therapies specifically for use in adults with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. The proposed population aligns with the current use of biologics for treating plaque psoriasis patients with the highest unmet need, and hence the expected use of bimekizumab within the NHS.[14]

A.5.2 Comparators

Cost comparison analysis is an appropriate framework for evaluation where treatments can be compared on the basis of differences in cost only. In the treatment of psoriasis with biologic therapies, costs are substantially influenced by response-based treatment discontinuation at the end of the initial treatment period.

In previous NICE technology appraisals for biologics, economic models have used the proportion of patients achieving a PASI 75 response to determine the discontinuation rate at the end of the initial period, in line with the guidance published by NICE for biologics.[16-20, 22, 24-26, 29, 30] As such, the most suitable comparators for a cost-comparison with bimekizumab would be those with a similar proportion of patients achieving at least a PASI 75 response at the end of the initial period, and thus similar rates of treatment discontinuation. Where PASI 75 response can be inferred to be similar, cost-comparison methods can be considered appropriate.

To assess this, an indirect comparison (network meta-analysis [NMA]) was conducted to estimate the PASI outcomes at the end of the initial period for bimekizumab relative to the full range of comparators

specified in the final scope. The network of evidence was based on a systematic literature review that identified relevant evidence across all treatments that might be used for the population in question. The NMA found bimekizumab [redacted]. As such, risankizumab, ixekizumab and brodalumab represent appropriate comparators for a cost-comparison analysis. This choice of comparators also means that bimekizumab is compared to the most recently approved biologic (risankizumab), the biologic most recently judged to be a cost-effective treatment option via cost comparison methodology (risankizumab), and other IL-17-targeting treatments (ixekizumab [IL-17 inhibitor] and brodalumab [IL-17 receptor inhibitor]). This comparator selection was also validated as representing reasonable clinical comparators to bimekizumab by clinical experts at an advisory board.[31] Whilst this represents a subset of the comparators specified in the final scope, precedent from both previous cost-comparison FTAs in this indication (TA521, TA596) supports that a cost-comparison does not need to be conducted versus all biologics.[25, 29]

It should be noted that the NMA found that patients treated with bimekizumab achieved [redacted] relative to all comparators included in the final scope, including risankizumab, ixekizumab and brodalumab. However, achievement of PASI 90 or PASI 100 does not impact ongoing treatment costs (continuation of treatment is determined by PASI 75, based on precedent from prior NICE appraisals in this indication). Therefore, whilst the superiority of bimekizumab on probability of achieving PASI 90 or PASI 100 serves to provide additional patient health benefit in terms of skin clearance, there is no additional ongoing treatment cost as there is for higher PASI 75 response rates. These higher rates of PASI 90 and PASI 100 response are therefore not considered relevant for inclusion in the cost comparison analysis framework.

An overview of the decision problem for this appraisal is presented in Table 3.

Table 3: The decision problem – B.1.1.2 (pages 9–12)

	Final scope issued by NICE[32]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate to severe plaque psoriasis.	Adult patients with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated.	Aligns with the recommendations made in previous NICE technology appraisals regarding biologics for the treatment of plaque psoriasis,[16-20, 22, 24-26, 29, 33] and thus with the current positioning of other biologics in the clinical pathway and expected use of bimekizumab in NHS clinical practice.[14]
Intervention	Bimekizumab.	Bimekizumab.	As per the draft SmPC.
Comparator(s)	If systemic non-biological treatment or phototherapy is suitable: • Systemic non-biological therapies (including methotrexate, ciclosporin and acitretin) • Phototherapy with or without psoralen If conventional systemic non-biological treatment (including methotrexate, ciclosporin and acitretin) and phototherapy are inadequately effective, not tolerated or contraindicated: • TNF-alpha inhibitors (adalimumab, etanercept, infliximab [for very severe plaque psoriasis, as defined by a total PASI of 20 or more, and a DLQI of more than 18] and certolizumab pegol) • IL-17 family inhibitors or receptor inhibitors (brodalumab, ixekizumab and secukinumab) • IL-23 inhibitors (guselkumab, tildrakizumab and risankizumab) • IL-12/IL-23 inhibitors (ustekinumab)	• Risankizumab • Ixekizumab • Brodalumab	Bimekizumab has robust evidence consistently demonstrating that it provides similar or greater health benefits than other biologic treatments for plaque psoriasis. • The BE VIVID, BE SURE and BE RADIANT active comparator-controlled trials, as well as results from a network meta-analysis (NMA), together provide direct and indirect evidence of statistically significantly higher PASI 90 and 100 response rates at Week 16 for bimekizumab versus all other biologics • Results from the NMA indicate that bimekizumab is likely to achieve [redacted], which were found to be ranked as the next most effective treatment options after bimekizumab. PASI 75 is the key determinant of ongoing treatment costs in a cost comparison.

	• Apremilast • Dimethyl fumarate • Best supportive care		As such, bimekizumab may be appropriately compared with risankizumab, ixekizumab, brodalumab through the FTA cost-comparison route due both to its similar or greater efficacy and similar or lower costs. This choice of comparators also means that bimekizumab is compared to the most recently approved biologic (risankizumab), which was assessed via the cost comparison methodology, as well as IL-17-targeting treatments (ixekizumab [IL-17 inhibitor] and brodalumab [IL-17 receptor inhibitor]). This comparator selection was validated as representing reasonable clinical comparators to bimekizumab by clinical experts at an advisory board.[31]
Outcomes	The outcome measures to be considered include: • Severity of psoriasis • Psoriasis symptoms, such as itch on the following areas: face, scalp, nails and joints, and other difficult-to-treat areas including the hands, feet and genitals • Mortality • Response rate • Duration of response • Relapse rate • Adverse effects of treatment • Health-related quality of life	• Severity of psoriasis, measured using PASI • Itch, pain and scaling, measured using PSD scores (published as P-SIM) [34] • Psoriasis symptoms on high impact and/or difficult-to-treat areas measured using scalp IGA, mNAPSI and pp-IGA • Response rate, measured using the PASI 90/100 and IGA 0/1 response rates as co-primary endpoints in the clinical trials included in this submission • Durable response, measured using the PASI 75/90/100 response rates	Psoriasis symptoms on the face and genitals have not been included in this submission due to data limitations. Mortality was included in the reporting of AEs in terms of clinical evidence base. General population mortality was reflected in the economic analysis.

		at the end of the study period • Relapse rate, measured using the proportion of Week 16 PASI 90 responders whose response subsequently falls below PASI 75 (for patients continuing on active treatment versus those re-randomised to placebo) • Adverse events • Health-related quality of life, measured using DLQI	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. For the comparators, the availability and cost of biosimilars should be taken into account.	A cost-comparison approach has been taken, with risankizumab, ixekizumab and brodalumab as comparators. The time horizon for assessing costs has been set to 10 years, aligning with both TA596 and TA521, the two previous cost-comparison appraisals in this indication.[27, 28] This should be a sufficient length of time to accurately assess the costs of the comparators, given the 20% annual discontinuation rate. Costs were considered from the NHS and Personal Social Services perspective. A PAS for bimekizumab has been included in the cost-comparison model. No public commercial arrangements are available for the comparators.	Bimekizumab is considered to be appropriate for assessment via cost-comparison FTA approach as it provides superior health benefits at similar or lower costs to risankizumab, ixekizumab and brodalumab. These are the most relevant comparators for bimekizumab as they have a similar PASI 75 response rate to bimekizumab at Week 16, as demonstrated by the NMA. PASI 75 is the determinant of treatment continuation at the end of the initial treatment period and hence the only efficacy input that impacts costs in a cost-comparison analysis.

Subgroups to be considered	Where the evidence allows, the following subgroups will be considered: • Previous use of phototherapy and systemic nonbiological therapy • Previous use of biological therapy • Severity of psoriasis (moderate, severe). Where the evidence allows, sequencing of different drugs and the place of bimekizumab in such a sequence will be considered. The availability and cost of biosimilar products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The following subgroup analyses are provided in Appendix E: • Any prior systemic therapy (yes/no) • Prior biologic exposure (yes/no) • Baseline disease severity (DLQI >10: yes/no) This submission takes a cost-comparison approach and therefore the model will not include treatment sequencing.	The decision not to include treatment sequencing is aligned with the approach taken in TA596 and ERG feedback from TA521.[27, 28]

Abbreviations: DLQI: Dermatology Life Quality Index; DMF: dimethyl fumarate; ERG: Evidence Review Group; EQ-5D: EuroQol - 5 dimensions; FAD: final appraisal determination; HRQoL: health-related quality of life; IGA: Investigator's Global Assessment; IL: interleukin; mNAPSI: modified Nail Psoriasis Severity Index; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PAS: patient access scheme; PASI: Psoriasis Area Severity Index; pp-IGA: palmoplantar Investigator's Global Assessment; PSD: patient symptom diary; P-SIM: Psoriasis Symptoms and Impacts Measure; SmPC: summary of product characteristics; TA: technology appraisal; TNF: tumour necrosis factor.
Source: NICE final scope.[32]

A.6 Clinical effectiveness evidence

Bimekizumab is the first biologic to present direct, head-to-head evidence versus three different biologic comparators with three different mechanisms of action at the time of NICE appraisal. The direct clinical evidence base for bimekizumab consists of four Phase III/IIIb RCTs (BE READY, BE VIVID, BE SURE and BE RADIANT), conducted in a total of 2,223 patients. A summary of these four studies is provided in Table 4. These studies provide a robust clinical evidence base to demonstrate the speed, depth and maintenance of responses to bimekizumab relative to multiple currently approved biologic treatments and are consistent in their demonstration of bimekizumab's efficacy and safety.

Table 4: Clinical effectiveness evidence – B.3.2 (pages 36–38)

Study	BE READY (NCT03410992)	BE VIVID (NCT03370133)	BE SURE (NCT03412747)	BE RADIANT (NCT03536884)
Study design	Phase III, multicentre, randomised, 56-week, double-blind fully placebo-controlled study, consisting of a 16-week initial treatment period followed by a randomised-withdrawal period	Phase III, multicentre, randomised, 52-week, double-blind study, placebo-controlled up to 16 weeks and active-controlled for the full study period	Phase III, multicentre, randomised, 56-week, double-blind study, active-controlled up to 24 weeks followed by a dose-blind maintenance period	Phase IIIb, multicentre, randomised, 48-week, double-blind, active-controlled study, consisting of a 16-week initial treatment period followed by a maintenance treatment period, with a subsequent optional 96-week open label extension period
Population	• ≥18 years of age • Plaque psoriasis for at least 6 months prior to the screening visit • PASI score ≥12, affected BSA ≥10% and IGA score ≥3 on a 5-point scale • Candidates for systemic therapy and/or phototherapy			
Intervention(s)	• Bimekizumab 320 mg Q4W for the 16-week initial treatment period, followed by re-randomisation to Q4W, Q8W, or placebo	• Bimekizumab 320 mg Q4W	• Bimekizumab 320 mg Q4W • Bimekizumab 320 mg Q4W for the 16-week initial treatment period followed by Q8W	• Bimekizumab 320 mg Q4W for the 16-week initial treatment period, followed by re-randomisation to Q4W or Q8W
Comparator(s)	• Placebo Q4W	• Placebo Q4W up to Week 16, followed by BKZ 320 mg Q4W • Ustekinumab, 45 mg for	• Adalimumab as an initial dose of 80 mg at Week 0, followed by 40 mg Q2W starting from Week 1 to Week 23, followed by BKZ	• Secukinumab 300 mg at Weeks 0, 1, 2, 3, 4 and Q4W thereafter

		patients ≤100kg and 90 mg for patients >100kg, at Weeks 0, 4 and Q12W thereafter	320 mg Q4W starting from Week 24	
Indicate if trial supports application for marketing authorisation	Yes	Yes	Yes	No
Indicate if trial used in the economic model	Yes	Yes	Yes	Yes
Rationale for use/non-use in the model	Trial is relevant for inclusion in the evidence network for indirect treatment comparison, and therefore informs relative effectiveness estimates for the model via the network meta-analysis.			
Reported outcomes specified in the decision problem	• Severity of psoriasis o Measured using PASI and IGA • Psoriasis symptoms on high impact areas o Measured using scalp IGA, pp-IGA and mNAPSI, • Mortality o Included in the reporting of AEs but not otherwise assessed • Response rate o Measured using PASI and IGA response rates • Durability of response o Measured using PASI and IGA response rates at the end of the study period (48–56 weeks) • Relapse rate o Measured using percentage of patients who relapsed during the randomised withdrawal period (available for BE READY only) • Adverse effects of treatment o Measured using incidence of TEAEs • Health-related quality of life			

	o Measured using DLQI
All other reported outcomes	• Response rates and change from baseline in the PSD items itch, pain, and scaling

Note: For treatments with contrasting dosing regimens, additional placebo doses were administered in order to maintain treatment blinding.
Abbreviations: AE: adverse event; CSR: clinical study report; IGA, Investigator's Global Assessment; mNAPSI: modified Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; pp-IGA, palmoplantar Investigator's Global Assessment; PSD: patient symptom diary; P-SIM: Psoriasis Symptoms and Impacts Measure; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; Q12W: every 12 weeks; TEAE: treatment-emergent adverse event;.
Source: Trial protocols and CSRs for BE READY, BE VIVID, BE SURE and BE RADIANT.[2-4, 8, 35-38]

A.6.1 Generalisability to the UK plaque psoriasis patient population

UK clinical experts consider that the patients enrolled in the bimekizumab trial population were generalisable to the UK psoriasis population; in particular, the relatively high PASI scores and the mix of patients with prior biologic experience were highlighted as representative.[31]

The baseline characteristics of the patients in the four bimekizumab trials were also found to be broadly similar to the characteristics of patients with psoriasis being treated with biologic therapy enrolled in the BADBIR registry (Document B, Section B.3.3.2).[39] Slight differences include a lower DLQI score, a slightly higher PASI score, a higher proportion of patients experiencing comorbid psoriatic arthritis and a higher proportion of male participants in the bimekizumab trials compared with the BADBIR patients. However, clinical advisors indicated that these differences were not likely to have a material impact on clinical effectiveness.[31]

The patients in these trials were therefore considered to be representative of adult patients in the UK with moderate-to-severe plaque psoriasis, thus supporting the generalisability of the clinical effectiveness data.

A.7 Key results of the clinical effectiveness evidence

A.7.1 Response rates by Week 16 (initial treatment period)

Bimekizumab demonstrated higher PASI 90 and PASI 100 response rates at Week 16 compared with placebo, ustekinumab, adalimumab and secukinumab

In direct, head-to-head trials, bimekizumab achieved higher response rates compared with placebo, ustekinumab, adalimumab [redacted] for both PASI 90 (all p<0.001; [redacted]) and PASI 100 (all p<0.001; p-value nominal for the comparison with ustekinumab) at Week 16. These endpoints represented the co-primary/primary endpoints of the bimekizumab clinical trials. Although PASI 75 is considered to be an adequate response, these higher response thresholds are considered to be more reflective of patients' treatment goals of complete or near complete clearance, with complete skin clearance representing an important way to reduce the impact of psoriasis on patients' daily life.[10-13, 40]

Bimekizumab also achieved higher PASI 75 response rates compared with placebo, [redacted] and adalimumab (all nominal p<0.001), [redacted].

A summary of all PASI 100, 90 and 75 response rates across trials is provided in Table 5.

Table 5: PASI response rates at Week 16 in BE READY, BE VIVID, BE SURE and BE RADIANT (RS [NRI]) – B.3.6.2 (page 68)

Outcome, n (%)	BE READY		BE VIVID			BE SURE		BE RADIANT	
	PBO (n=86)	BKZ (n=349)	PBO (n=83)	BKZ (n=321)	UST (n=163)	BKZ (n=319)	ADA (n=159)	BKZ (n=373)	SEC (n=370)
PASI 75 at Week 16	2 (2.3)	333 (95.4)	[redacted]	[redacted]	[redacted]	295 (92.5)	110 (69.2)	[redacted]	[redacted]
PASI 90 at Week 16	1 (1.2)	317 (90.8)	4 (4.8)	273 (85.0)	81 (49.7)	275 (86.2)	75 (47.2)	[redacted]	[redacted]
PASI 100 at Week 16	1 (1.2)	238 (68.2)	0	188 (58.6)	34 (20.9)	194 (60.8)	38 (23.9)	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BKZ, bimekizumab; IGA, Investigator's Global Assessment; NRI: non-responder imputation; PASI, Psoriasis Area and Severity Index; PBO, placebo; RS: randomised set; SEC, secukinumab; UST, ustekinumab.
Source: CSRs for BE READY, BE VIVID, BE SURE and BE RADIANT.[2-4, 8]

[redacted].

Bimekizumab exhibited a rapid treatment response by Week 4, demonstrating efficacy from the first dose

Across the four clinical trials, a high proportion of patients receiving bimekizumab showed a substantial response to treatment after receiving only a single dose. This was demonstrated by PASI 75 response of ≥71% at Week 4, which was a pre-specified secondary outcome in all four clinical trials. Bimekizumab achieved significantly higher PASI 75 responses at Week 4 than placebo, ustekinumab, adalimumab [redacted] (all [redacted]; Document B, Section B.3.6.2). These results support a more rapid onset of treatment effect on PASI response for bimekizumab versus the trial comparators.

Bimekizumab demonstrated higher IGA 0/1 response rates at Week 16 compared with placebo, ustekinumab, adalimumab and secukinumab

IGA 0/1 response represented one of the co-primary endpoints in BE READY, BE VIVID and BE SURE, and was defined as a score of 'clear' or 'almost clear' with at least a 2-category improvement from baseline. IGA 0 was defined as a score of 'clear' with at least a 2-category improvement from baseline. Across the four trials, at Week 16 bimekizumab achieved significantly higher response rates for IGA 0/1 compared with placebo, ustekinumab, adalimumab (all p<0.001)
[redacted].

A.7.2 Response rates at the final visit (Weeks 48–56)

The rapid and high level of complete skin clearance achieved with bimekizumab, which extends to high-impact areas such as nails, scalp, palms and soles (Document B, Section B.3.6.2 for evidence on high-impact areas), is maintained over time with 8-week dosing.

Response to treatment with bimekizumab was assessed in the head-to-head clinical trials up to 48–56 weeks. BE VIVID and BE SURE included PASI 90 at the final visit (Week 52 and 56, respectively) as a secondary outcome, while BE RADIANT included PASI 100 at the final visit (Week 48) as a secondary outcome. In all three trials, PASI 90 and PASI 100 response rates remained high at the final visit, demonstrating durability of response to bimekizumab (Table 6). Bimekizumab achieved higher PASI 90 responses compared with ustekinumab at Week 52 (BE VIVID; p<0.001) [redacted]. Bimekizumab also achieved higher PASI 100 responses compared with ustekinumab at Week 52 (BE VIVID; nominal p<0.001) and secukinumab at Week 48 (BE RADIANT; [redacted]).

Table 6: PASI 90, PASI 100 and IGA 0/1 response rates at final visit – B.3.6.3 (page 72)

Response, n (%)	BE VIVID Week 52 (RS [NRI])		BE SURE Week 56 (RS [NRI])			BE RADIANT Week 48			
						(MS [NRI])		(RS [NRI])	
	BKZ Q4W (n=321)	UST (n=163)	BKZ Q4W/Q8W (n=161)	BKZ Q4W (n=158)	BKZ Total (n=319)	BKZ Q4W/Q8W (n=215)	BKZ Q4W (n=147)	BKZ Total (n=373)	SEC (n=370)
PASI 90 at final visit	[redacted]	[redacted]	133 (82.6)	134 (84.8)	267 (83.7)	[redacted]	[redacted]	[redacted]	[redacted]
IGA 0/1 at final visit	[redacted]	[redacted]	134 (83.2)	130 (82.3)	264 (82.8)	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100 at final visit	[redacted]	[redacted]	113 (70.2)	114 (72.2)	227 (71.2)	[redacted]	[redacted]	[redacted]	[redacted]

Footnote: BE READY is not included in this table as only patients achieving a PASI 90 response at Week 16 continued on to the randomised withdrawal period and thus response rates at the final visit are not comparable to the other trials. In BE VIVID the placebo-controlled period ended at Week 16 and in BE SURE treatment with adalimumab ended at Week 24, so no values are available at the time of the final visit for the BE VIVID placebo arm and BE SURE adalimumab arm. For BE RADIANT, statistical comparisons of BKZ versus SEC at Week 48 as reported in the text preceding the table are based on the RS data reported in the table. BE RADIANT response rates by BKZ dose are also provided in Table 6 to demonstrate consistency in efficacy between the two BKZ maintenance doses evaluated in the trial; these are provided for the MS rather than the RS, as randomisation to Q4W or Q8W occurred at Week 16 and some patients included in the RS discontinued treatment prior to Week 16.
Abbreviations: CI: confidence interval; UST: ustekinumab; BKZ: bimekizumab; IGA: Investigator's Global Assessment; MS: maintenance set; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; Q4W: every 4 weeks; Q8W every 8 weeks; RS: randomised set.
Source: CSRs for BE VIVID, BE SURE and BE RADIANT.[2-4]

A.7.3 Health-related quality of life: DLQI 0/1 response rates

Bimekizumab provided substantial improvements in HRQoL by Week 16, with a majority of patients' daily lives no longer impacted by their psoriasis

The high rates of durable skin clearance achieved with bimekizumab treatment are expected to support improvements in patients' quality of life and ability to carry out their everyday lives without the burden of their psoriasis. In the bimekizumab clinical trials, this is evidenced by improvements in DLQI 0/1 (no impact of skin symptoms on daily living) response rates with bimekizumab treatment.

In both BE READY and BE VIVID, at Week 16 patients treated with bimekizumab showed a [redacted]

Figure 2: DLQI 0/1 response rate at Week 16 across BKZ trials (RS [NRI]) – B.3.6.9 (page 70)

Footnotes: *** p<0.001. DLQI 0/1 response rate was not included in the testing hierarchy for any of the trials and thus comparisons were not controlled for multiplicity, all p-values are therefore nominal p-values. For BE SURE, the BKZ Q4W and the BKZ Q4W/Q8W arms were combined for this analysis as all patients received BKZ Q4W through to week 16.
Abbreviations: BKZ, bimekizumab; CSR: clinical study report; DLQI, Dermatology Life Quality Index; NRI: non-responder imputation; PBO, placebo; RS: randomised set.
Source: CSRs for BE READY, BE VIVID, BE SURE and BE RADIANT.[2-4, 8]

Patients treated with bimekizumab also showed [redacted]. In BE VIVID, at Week 52 bimekizumab achieved a [redacted]. Similarly, in BE RADIANT, at Week 48 bimekizumab achieved a

[redacted]. In BE SURE, treatment with adalimumab ended at Week 24, so no values are available at the time of the final visit for the adalimumab arm.

A.7.4 Adverse reactions

Bimekizumab was found to be well-tolerated and demonstrated a safety profile consistent with that of anti-IL-17A biologics, with no new safety signals identified. Bimekizumab dosing regimens had an acceptable safety profile with a risk of treatment-emergent adverse events that did not increase with longer exposure.

The IL-17 pathway is recognised as playing a role in defence against candida species, resulting in increased oral candidiasis infections in patients treated with anti-IL-17 biologics compared with placebo.[41, 42] The incidence of oral candidiasis has been observed to be higher with bimekizumab than has been observed with other anti-IL-17 class biologics. However, very few patients who experienced oral candidiasis while receiving bimekizumab discontinued treatment as the vast majority of cases were mild to moderate (>99%) and easily managed with standard anti-fungal therapy.

A.8 Evidence synthesis

NMA methodology was used for the indirect comparison of bimekizumab with other systemic therapies for the treatment of moderate-to-severe psoriasis. The NMA included all treatments specified in the final NICE scope, in order to be comprehensive in the evidence considered, and the evidence base informing the NMA was identified from a systematic literature review. An NMA was conducted for outcomes of PASI response rates (PASI 50, 75, 90 and 100) for evaluation of relative effectiveness. For evaluation of relative safety, NMAs were conducted for outcomes of serious adverse events and adverse events due to discontinuation. All outcomes were assessed at a timepoint range of 10-16 weeks, as per the timepoint used for the primary endpoint of the respective trials, and consistent with the approach taken in the NMA for the most recent NICE appraisal in this indication (risankizumab, TA596).[27]

The NMA of PASI response rates found that bimekizumab was associated with similar or greater clinical efficacy compared with alternative biologics approved for the treatment of moderate to severe plaque psoriasis. A forest plot presenting the probabilities of achieving each PASI outcome (and associated credible intervals) for the base case NMA (baseline risk-adjusted, random effects, allowing for relaxation of the proportional treatment effects assumption) is presented in Figure 3.

These results found bimekizumab to be associated with the [redacted]. For the PASI 75 outcome, bimekizumab was [redacted]

Figure 3: Forest plot of probabilities of achieving at least the given PASI response for each intervention at 10–16 weeks – B.3.9.6 (page 86)

Abbreviations: kg: kilograms; mg: milligrams; PASI: Psoriasis Area and Severity Index.

The NMAs of serious AEs and discontinuation due to AEs found [redacted] between bimekizumab and any of the biologic treatments can be inferred for either outcome, therefore supporting that bimekizumab and other biologics are associated with similar safety profiles in terms of adverse events likely to significantly impact patient quality of life, incur NHS resource use or trigger treatment discontinuation.

A.9 Overview of the cost-comparison analysis

A cost-comparison analysis was conducted to evaluate the cost to the NHS of using bimekizumab versus brodalumab, ixekizumab and risankizumab to treat adult patients with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. This analysis ultimately demonstrated that bimekizumab offers superior health benefits for patients at similar or lower costs to the comparator therapies.

An overview of the costs and assumptions informing the cost-comparison analysis is provided in Table 7.

Table 7: Costs and assumptions in the cost-comparison analysis

Costs and assumptions	Source	Justification
Drug acquisition costs	UCB Pharma Ltd (bimekizumab), BNF (comparators)	Source of drug costs on the NHS
No other costs included in the analysis	TA521, TA596, Company NMA (Section B.3.9)	Bimekizumab, risankizumab, ixekizumab and brodalumab are all subcutaneously administered therapies and it is expected they will therefore be associated with the same administration and monitoring requirements. The cost-comparison assumed equal efficacy (PASI ≥75 response) and no differences in adverse events that would impact costs between bimekizumab and the comparator biologics, supported by the results of the NMA presented in Section B.3.9. Inclusion of only drug acquisition costs is consistent with both prior cost-comparison NICE appraisals in this indication (TA521, TA596).
Time horizon of 10 years	TA521, TA596	A time horizon of 10 years was preferred in both prior cost-comparison NICE appraisals in this indication (TA521, TA596). A time horizon of 5 years was explored in a scenario analysis.
Annual probability of discontinuation from maintenance treatment is the same for all biologics (20%)	Prior NICE TAs, including TA596, TA575, TA574, TA521	This assumption is aligned with both prior cost-comparison NICE appraisals in this indication (TA521, TA596). An annual probability of discontinuation of 20% has also been used in a number of more recent NICE single technology appraisals (e.g. TA575, TA574).

Abbreviations: BNF: British National Formulary; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; PASI: Psoriasis Area and Severity Index; TA: technology appraisal.
Source: Committee papers for TA521, TA574, TA575 and TA596.[15, 27, 28, 43]

A.10 Base-case results

Table 8 reports the results of the base case cost-comparison analysis at list price for bimekizumab. Table 9 reports the results of the base case cost-comparison analysis at the PAS price for bimekizumab. Confidential PAS discounts for comparators are not included in either analysis as these are not publicly known.

Table 8: Base-case results with bimekizumab at list price – B.4.3 (page 105)

Technologies	Total costs over 10 years	Cost difference: bimekizumab minus comparator
Bimekizumab	[redacted]	
Brodalumab	£65,769.52	[redacted]
Ixekizumab	£62,304.35	[redacted]
Risankizumab	£62,384.76	[redacted]

Footnotes: Costs reported over a 10-year time horizon. Positive cost differences indicate that bimekizumab is associated with higher costs than the comparator; negative cost differences indicate that bimekizumab is cost saving versus the comparator.

Table 9: Base-case results with bimekizumab at PAS price – B.4.3 (page 105)

Technologies	Total costs over 10 years	Cost difference: bimekizumab minus comparator
Bimekizumab	[redacted]	
Brodalumab	£65,769.52	[redacted]
Ixekizumab	£62,304.35	[redacted]
Risankizumab	£62,384.76	[redacted]

Footnotes: Costs reported over a 10-year time horizon. Positive cost differences indicate that bimekizumab is associated with higher costs than the comparator; negative cost differences indicate that bimekizumab is cost saving versus the comparator.

A.11 Key sensitivity and subgroup analyses

Deterministic sensitivity analysis (one-way sensitivity analysis) explored the impact of varying key uncertain model parameters (annual probability of discontinuation, discount rate, assumed PASI ≥75 response rate applied to all therapies) within lower and upper bounds. Scenario analyses explored the impact of using a 5-year time horizon, excluding general population mortality, and assuming alternative annual probabilities of discontinuation that were also explored in TA596. These sensitivity analyses found the results to be robust to changes in the model parameters investigated. No subgroup analyses were performed as no differences in efficacy are expected across subgroups for bimekizumab versus its comparators.

A.12 Interpretation and conclusions of the evidence

The clinical efficacy and safety of bimekizumab has been demonstrated in four Phase III/IIIb RCTs, BE READY, BE VIVID, BE SURE and BE RADIANT, all of which successfully met all of their primary and secondary endpoints included in the testing hierarchy. Bimekizumab is the first biologic to present direct, head-to-head evidence versus three different biologic comparators with three different mechanisms of action at the time of NICE appraisal. These trials were international, multicentre, double blind, controlled studies, including a total of 2,223 adult patients with moderate to severe plaque psoriasis. These trials therefore provide a robust clinical evidence base across a broad population of moderate to severe plaque psoriasis patients, with generalisability to the UK moderate to severe plaque psoriasis population. These studies are consistent in their demonstration of the efficacy and safety profile of bimekizumab.

The results from the active comparator-controlled trials, together with an NMA, provide both direct and indirect evidence of consistently statistically significantly greater PASI 90 and PASI 100 response rates at Week 16 for bimekizumab versus all other treatments licensed for the treatment of plaque psoriasis. These high rates of complete skin clearance, which extend to high-impact areas such as nails, scalp, palms and soles, have been demonstrated to be durable and maintained over time with the Q8W maintenance dosing regimen. The impact on patients of these high rates of durable skin clearance is supported by evidence of substantial improvements in QoL with most patients' daily lives no longer impacted by their psoriasis.

In addition to its clinical effectiveness profile, bimekizumab was found to be well-tolerated with a risk that did not increase with longer exposure, and demonstrated a safety profile consistent with that of other anti-IL-17A biologics. As expected given the mechanism of action of bimekizumab, there was an elevated risk of oral candidiasis while receiving bimekizumab, however, the vast majority of cases were mild to moderate ([redacted]), did not lead to treatment discontinuation and were likely to have a minimal impact on costs and HRQoL.[41, 42]

The cost-comparison analysis assessed the costs of bimekizumab compared with risankizumab, ixekizumab and brodalumab. The results of this analysis demonstrate that [redacted]. This analysis included costs associated with treatment acquisition, modelled bimekizumab at list price and PAS price, and comparators at list price. Results of deterministic sensitivity analysis and scenario analyses demonstrated these findings to be robust to uncertainty in key model parameters.

The cost comparison is based on evidence that a similar proportion of patients treated with bimekizumab and these comparators will achieve an adequate response (PASI 75) and continue incurring treatment costs. Of those patients who meet this threshold for treatment continuation, a higher proportion are expected to achieve PASI 90 or PASI 100 with bimekizumab. Achievement of these higher rates of clearance provides additional benefit to patients in meeting their desired treatment goals.

Overall, the cost comparison analysis demonstrated that bimekizumab offers superior health benefits for patients with moderate to severe plaque psoriasis at similar or lower costs to the comparator therapies.

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Fast track appraisal: cost-comparison case

ID2692 Bimekizumab for the treatment of moderate to severe plaque psoriasis

12 May 2021: UCB Pharma Limited memo to NICE (summary amendments to Company Evidence originally submitted to NICE 12th January 2021)

The following two amendments have been made by UCB Pharma to the original company evidence submission for the appraisal of bimekizumab for the treatment of moderate to severe plaque psoriasis:

- **<u>Amendment 1</u>: Revised wording related to method of administration and dosage**:

  The wording has been amended as follows, in line with the UCB update communicated to NICE and ERG in response to the ERG report April 2021:

  [redacted]

  Impact of Amendment 1 on results of the company base case, sensitivity, and scenario analyses: None

- **<u>Amendment 2</u>: Revised bimekizumab fixed net price and percent discount from list price:**

  The fixed net price and percentage discount has been amended as follows:

  [redacted]

  Impact of Amendment 2 on results of the company base case, sensitivity, and scenario analyses:

  Base-case results

  Error! Reference source not found. *presents the base case results over the 10-year time horizon at list price for bimekizumab.*

Table 1: Base case results – bimekizumab at list price

Therapy	Total cost over 10 years	Cost difference: bimekizumab minus comparator
Bimekizumab (list price)	[redacted]	-
Brodalumab	£65,769.52	[redacted]
Ixekizumab	£62,304.35	[redacted]
Risankizumab	£62,384.76	[redacted]

Footnotes: *Positive cost differences indicate that bimekizumab is associated with higher costs than the comparator; negative cost differences indicate that bimekizumab is cost saving versus the comparator.*

Error! Reference source not found. *presents the base case results over the 10-year time horizon at PAS price for bimekizumab. The total drug costs with bimekizumab at PAS price over this time horizon were* [redacted]*, corresponding to a* [redacted].

Table 2: Base case results – bimekizumab at PAS price

Therapy	Total cost over 10 years	Cost difference: bimekizumab minus comparator
Bimekizumab (PAS price)	[redacted]	-
Brodalumab	£65,769.52	[redacted]
Ixekizumab	£62,304.35	[redacted]
Risankizumab	£62,384.76	[redacted]

Abbreviations: *PAS: patient access scheme.*
Footnotes: *Positive cost differences indicate that bimekizumab is associated with higher costs than the comparator; negative cost differences indicate that bimekizumab is cost saving versus the comparator.*

Sensitivity and scenario analyses

Deterministic sensitivity analysis (one-way sensitivity analysis)

Deterministic sensitivity analysis was performed to test the sensitivity of the model's results to the uncertainty surrounding certain input parameters. Each

relevant input was varied to its specified lower and upper bound in turn, whilst all other parameters were held constant. The discount rate was varied between 0% and 3.5%, whilst the PASI 75 response rate that is applied to all treatments was varied between the lower and upper credible intervals for the bimekizumab PASI 75 response rate from the NMA. For the annual discontinuation rate of 20% no confidence intervals were available, and this was therefore varied by ±20% of the base case value. Drug acquisition costs were not included in the DSA as these are not associated with uncertainty.

Error! Reference source not found. *to* ***Error! Reference source not found.*** *display tornado diagrams of results of the DSA for the cost-comparison of bimekizumab at PAS price with each of the four comparators. The results of the DSA showed that the biggest driver of results was the annual probability of discontinuation applied across biologics. In contrast, the PASI 75 response rate efficacy parameter had less of an influence on model results.*

Equivalent tornado diagrams for the analyses of bimekizumab at list price can be found in Appendix J.

Figure 1: Tornado diagram – comparison of bimekizumab (PAS price) to brodalumab (list price)

Abbreviations: *PAS: patient access scheme; PASI: Psoriasis Area and Severity Index.*

Footnotes: *The indicated "change to the base case cost difference" should be added to the base case cost difference reported in* ***Error! Reference source not found.*** *in order to understand the new cost difference under the sensitivity analysis parameter. A negative change to the base case cost difference in the tornado diagram indicates that the sensitivity analysis favours bimekizumab, relative to the base case. Conversely, a positive change to the base case cost difference in the tornado diagram indicates that the sensitivity analysis favours the comparator, relative to the base case.*

Figure 2: Tornado diagram – comparison of bimekizumab (PAS price) to ixekizumab (list price)

Abbreviations: *PAS: patient access scheme; PASI: Psoriasis Area and Severity Index.*

Footnotes: *The indicated "change to the base case cost difference" should be added to the base case cost difference reported in* ***Error! Reference source not found.*** *in order to understand the new cost difference under the sensitivity analysis parameter. A negative change to the base case cost difference in the tornado diagram indicates that the sensitivity analysis favours bimekizumab, relative to the base case. Conversely, a positive change to the base case cost difference in the tornado diagram indicates that the sensitivity analysis favours the comparator, relative to the base case.*

Figure 3: Tornado diagram – comparison of bimekizumab (PAS price) to risankizumab (list price)

Abbreviations: *PAS: patient access scheme; PASI: Psoriasis Area and Severity Index.*
Footnotes: *The indicated "change to the base case cost difference" should be added to the base case cost difference reported in* ***Error! Reference source not found.*** *in order to understand the new cost difference under the sensitivity analysis parameter. A negative change to the base case cost difference in the tornado diagram indicates that the sensitivity analysis favours bimekizumab, relative to the base case. Conversely, a positive change to the base case cost difference in the tornado diagram indicates that the sensitivity analysis favours the comparator, relative to the base case.*

Scenario analysis

Error! Reference source not found. *summarises the scenario analyses that were explored in the model and the results of these scenario analyses for bimekizumab at PAS price. An equivalent table for the scenario analyses of bimekizumab at list price is provided in Appendix J.*

Table 3: Results of scenario analyses for bimekizumab at PAS price

Model feature	***Scenario***	***Difference in cost: bimekizumab minus comparator***		
		Brodalumab	***Ixekizumab***	***Risankizumab***
Base case		[redacted]	[redacted]	[redacted]
Time horizon	*5 years*	[redacted]	[redacted]	[redacted]
Mortality	*Exclude mortality*	[redacted]	[redacted]	[redacted]

Treatment discontinuation	*Warren et al. 2015 (11%)*[163]	[redacted]	[redacted]	[redacted]
	TA511 (18.7%)[161]	[redacted]	[redacted]	[redacted]
	Egeberg et al. 2018 (19%)[164]	[redacted]	[redacted]	[redacted]

Abbreviations: *PAS: patient access scheme.*
Footnotes: *Positive cost differences indicate that bimekizumab is associated with higher costs than the comparator; negative cost differences indicate that bimekizumab is cost saving versus the comparator*

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Fast track appraisal: cost-comparison case

ID2692 Bimekizumab for the treatment of moderate to severe plaque psoriasis

8 June 2021: UCB Pharma Limited Memo to NICE
(Data Update to Company Evidence Originally submitted to NICE 12th January 2021)

The below [Amendment 1 dated 12th May 2021] was made by UCB Pharma to the original company evidence submission for the appraisal of bimekizumab for the treatment of moderate to severe plaque psoriasis:

<u>Amendment 1</u>: Revised wording related to method of administration and dosage:

The wording has been amended as follows, in line with the UCB update communicated to NICE and ERG in response to the ERG report April 2021:

[redacted]

Impact of Amendment 1 on results of the company base case, sensitivity, and scenario analyses: None

<u>Additional Data 8th June 2021:</u> [redacted]

In light of the above amendment, UCB Pharma Ltd has now received additional data which may be pertinent to the appraisal of bimekizumab with respect to potential use [redacted]

[redacted] - these are presented below.

[redacted]

Table 1:

[redacted]

[redacted]

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Single technology appraisal

Bimekizumab for treating moderate to severe chronic plaque psoriasis ID2692

Clarification questions

9th February 2021

File name	Version	Contains confidential information	Date
		Yes/no	

Notes for company

Highlighting in the template

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.

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Section A: Clarification on effectiveness data

Proposed positioning of bimekizumab

A1. PRIORITY QUESTION. Please clarify which group of patients are referred to in the proposed marketing authorisation with respect to '[redacted] described in CS B.1.1.1. The ERG notes that in CS Table 2 a slightly different wording is used: '[redacted]' Please confirm which is correct and further clarify the difference between the type of patients who would be included within the marketing authorisation/pivotal trials and the narrower population specified in the company's decision problem.

[Company: please enter your answer to this question here]

A2. PRIORITY QUESTION. It is stated in CS Table 1 that the company's decision problem relates to adults with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated, and that this aligns with recommendations in previous NICE technology appraisals regarding biologics for the treatment of plaque psoriasis. However, previous NICE recommendations do not include patients with moderate disease (CS Table 4), and it is stated in CS B.1.4.3 that the proposed positioning of bimekizumab is

restricted to people with severe disease. Please clarify whether the company's decision problem does include people with moderate as well as severe disease.

[Company: please enter your answer to this question here]

A3. In Appendix D.2, please clarify what 'completion' and 'discontinuation' refer to - do these terms refer to completion/discontinuation of study treatment or the study itself?

[Company: please enter your answer to this question here]

Pivotal phase III bimekizumab trials

A4. Table 16 in Appendix D.3 states that "study participants received placebo injections at certain visits in order to maintain the blind".

- For BE-VIVID, please confirm whether this means that patients randomised to ustekinumab arms were also given placebo injections every 4 weeks to maintain the blinding.
- In BE-SURE, were the initial and Q2W adalimumab doses masked by giving placebo injections to patients at corresponding timepoints in the other trial arms?
- In BE-RADIANT were the initial weekly secukinumab doses masked by giving patients placebo injections at the corresponding time points in the other trial arms?
- Similarly, in BE-READY, BE-SURE and BE-RADIANT, please confirm that patients allocated to bimekizumab Q8W also received placebo injections every 4 weeks?

[Company: please enter your answer to this question here]

A5. The CS Table 13 describes sensitivity analyses using different imputation methods for missing outcome data. Please provide a summary of the results of these

sensitivity analyses or provide a description of how these results compared to the primary analyses.

[Company: please enter your answer to this question here]

A6. Please clarify how the odds ratios have been calculated for the subgroup analyses presented in Appendix E?

[Company: please enter your answer to this question here]

A7. The submission reports that the results of the phase III BE BRIGHT study are not available currently. Please indicate the timeframe for availability of the results.

[Company: please enter your answer to this question here]

Network meta-analysis

A8a. Please describe how the risk of bias assessments for the pivotal trials and trials included in the NMA were conducted – how many reviewers performed the assessments (e.g. two independent reviewers for each study) and how conflicts were resolved?

[Company: please enter your answer to this question here]

A8b. We note that a different set of quality criteria were used to assess the quality of the bimekizumab phase III trials compared to the risk of bias criteria used to assess the studies included in the network meta-analysis. Please elaborate on the origin/provenance of the latter set of criteria, and comment on whether/how the criteria assess two key dimensions of bias - allocation concealment and blinding.

[Company: please enter your answer to this question here]

A9. PRIORITY QUESTION. We note the statement: "An indirect treatment comparison in the ITT population was considered reasonable as characteristics such as outcome definitions, timepoints and analysis populations were fairly consistent across trials of treatments identified by the SLR" (Document B, page 89). Please summarise any evidence/clinical consensus on treatment effect modifiers in psoriasis, and describe the

distribution of any such effect modifiers across the included NMA trials (in relation to potential clinical heterogeneity).

[Company: please enter your answer to this question here]

A10. The submission states that "It should be noted that the results of the NMA presented in this submission and that of the NMA conducted for TA596 would not be expected to necessarily be the same, given that the NMA presented here includes a number of additional studies published since NICE appraisal TA596 was conducted". Apart from the pivotal phase III trials of bimekizumab, please cite or briefly summarise the key characteristics of other additional studies published since TA596 (e.g. intervention and comparator).

[Company: please enter your answer to this question here]

A11. PRIORITY QUESTION. Please provide the rationale for the development of the REZ model and the relaxation of the proportional treatment effects assumption. Is there any real-world evidence that the proportional treatment effects assumption is violated?

[Company: please enter your answer to this question here]

A12. PRIORITY QUESTION. Please provide the trial data used in the WinBUGS REZ model, together with an explanation of any imputation. Please provide the data as formatted for running with the WinBUGS code.

[Company: please enter your answer to this question here]

A13. PRIORITY QUESTION. Please provide the WinBUGS code used for the standard multinomial probit random effects model.

[Company: please enter your answer to this question here]

A14. PRIORITY QUESTION. Please clarify whether the baseline risk model was run for PASI-75 (as suggested by Figure 2, Appendix D) or PASI-50 as suggested by Appendix D.1.5. Please provide (i) the results for the baseline risk model, (ii) the WinBUGS code used for the baseline risk model, and (iii) the data used in the model, together with an explanation of any imputation.

[Company: please enter your answer to this question here]

A15. Please provide methods and results of the assessment of inconsistency in each of the NMA models.

[Company: please enter your answer to this question here]

A16. Was any consideration given to conducting an NMA for the maintenance period of the trials, in addition to the initial (induction) treatment period? How might this inform the NICE appraisal committee's decision making, in the company's opinion?

[Company: please enter your answer to this question here]

A17. Please consider repeating the NMA for the DLQI outcome. The DLQI and PSAI address complimentary aspects of psoriasis and an indirect comparison of bimekizumab with existing treatments on both of these measures may provide a more comprehensive assessment of efficacy.

[Company: please enter your answer to this question here]

A18. PRIORITY QUESTION. Please justify the choice of somewhat informative priors for the random effect standard deviation, Uniform(0,1), and square root SD around the probit thresholds, Uniform(0,0.5), rather than the traditional vague Uniform(0,5) in the REZ model. Also BetaPlac (baseline placebo effect on probit scale?) in the WinBUGS code (Figure 4, Appendix D) has a narrower Normal(0,100) than is traditionally accepted as vague. Please report the posterior estimates for each of these parameters.

[Company: please enter your answer to this question here]

A19. Please also explain the calculation of A ~ dnorm(0.919,268.744961031981) in the REZ model code (Figure 4, Appendix D). Is this the baseline risk on the probit scale?

[Company: please enter your answer to this question here]

A20. PASI response outcomes from the NMA are presented in terms of absolute probabilities. Please could the company present PASI response as relative risks to facilitate comparisons with other NMAs.

[Company: please enter your answer to this question here]

A21. Was a probit link considered as an alternative scenario to the binomial logit model for the safety endpoints?

[Company: please enter your answer to this question here]

Section B: Clarification on cost-comparison data

B1. PRIORITY QUESTION: CS Table 2 states that

[redacted]

. Please report the proportion of patients in the BE READY, BE VIVID, BE SURE and BE RADIANT trial populations [redacted]. Please also conduct a scenario analysis to estimate the impact on the costs of bimekizumab if all patients who met this criteria

[redacted]**.**

[Company: please enter your answer to this question here]

Section C: Textual clarification and additional points

C1. It is stated in B.4.2.1 that the population for the cost comparison is adult patients with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. This is not consistent with the proposed use of specified in CS section B.1.1.1, which is restricted to severe disease. Please clarify the target population for the cost-comparison.

[Company: please enter your answer to this question here]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Bimekizumab for treating moderate to severe chronic plaque psoriasis ID2692

Clarification questions

Company response

24th February 2021

File name	Version	Contains confidential information	Date
ID2692_Bimekizumab for psoriasis_UCB Pharma_Response to ERG clarification questions_24.02.21	1	Yes	24.02.2021

Section A: Clarification on effectiveness data

Proposed positioning of bimekizumab

A1. PRIORITY QUESTION. Please clarify which group of patients are referred to in the proposed marketing authorisation with respect to [redacted] described in CS B.1.1.1. The ERG notes that in CS Table 2 a slightly different wording is used: [redacted] Please confirm which is correct and further clarify the difference between the type of patients who would be included within the marketing authorisation/pivotal trials and the narrower population specified in the company's decision problem.

UCB response:

UCB expect bimekizumab to be used in the same population as previously recommended biologics and it is this population the decision problem aims to address.

The marketing authorisation for bimekizumab is expected to be for [redacted]

The population specified in the decision problem is narrower than the expected marketing authorisation, specifically considering bimekizumab for the treatment of moderate to severe plaque psoriasis in patients for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. This narrower population is believed to reflect the appropriate positioning for bimekizumab as it is the population considered in the majority of previous appraisals for biologics in plaque psoriasis. Please see the response to question A2 for a discussion of the precedent regarding the use of the phrase 'moderate to severe' in this context.

More specifically, the recommendations included in the final appraisal determinations (FADs) for the majority of previously approved biologics in plaque psoriasis (TA103, TA146, TA180, TA350, TA442, TA511, TA521, TA574, TA575, TA596) state that biologics should be used for the treatment of adults with plaque psoriasis when:[2-11]

- The disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 and
- The disease has not responded to other systemic treatments, including ciclosporin, methotrexate and phototherapy, or these options are contraindicated or not tolerated.

This is the same population as UCB aim to address with their decision problem, as bimekizumab is expected to be used in the same patient population as these previously recommended biologics.

The bimekizumab clinical trials that supported the marketing authorisation recruited a population of patients with a PASI ≥12, a body surface area (BSA) affected by psoriasis of ≥10% and an IGA score ≥3 on a 5-point scale. No minimum DLQI requirement was included in the trial eligibility criteria; however, mean DLQI at baseline was >10 across all patients in the four clinical trials (see baseline characteristics in Section B.3.3.2 of company submission Document B). Therefore, the trial populations represent patients who were likely to have severe psoriasis as per the definition from NICE FADs described above. The inclusion criteria for the clinical trials required that patients "must be a candidate for systemic therapy or phototherapy". This is [redacted] broader than the decision problem addressed in the submission, as patients were not required to have not responded to, been intolerant of or contraindicated for systemic therapy.

However, it is believed that the clinical trial population is sufficiently applicable to the decision problem population and representative of psoriasis patients likely to be treated with bimekizumab in UK clinical practice for the following reasons:

1. A comparison of the clinical trial populations with data from the BADBIR registry indicates good alignment between patient characteristics in the trials and biologic-eligible psoriasis patients in the UK (section B3.3.2; Figure 6).[12] Furthermore, clinical advisors indicated that any differences between the populations of the bimekizumab clinical trials and the BADBIR registry were not likely to have a material impact on clinical effectiveness.[13]

2. The psoriasis severity inclusion criteria for the bimekizumab trials are aligned with the clinical trials used to support previous appraisals for biologics in psoriasis. For example, the clinical trials supporting both the company submissions for risankizumab and guselkumab required that patients have PASI ≥12, sPGA/IGA ≥3, and involved BSA ≥10%.[1, 14] Although the bimekizumab trials did not specify a DLQI-based inclusion criteria, mean DLQI at baseline was at or above the DLQI score specified in the NICE definition of severe psoriasis.

3. There is precedent from previous appraisals for the inclusion of candidates for systemic therapy in clinical trial populations. For example, the most recent submissions for biologics in plaque psoriasis, risankizumab and tildrakizumab, specify in the trial inclusion criteria that enrolled patients must be a "prior candidate for phototherapy or systemic treatment for psoriasis" and "considered to be a candidate for phototherapy or systemic therapy", respectively. Neither submission reported that patients were required to have previously not responded to, been intolerant of or contraindicated for systemic therapy in order to be included in the clinical trials.[1, 15]

4. A subgroup analysis was carried out to investigate the impact of receiving any prior systemic therapy (including biologics, non-biologic systemics or phototherapy) on PASI response rates (Appendix E of the company submission). This analysis demonstrated that
[redacted]

[redacted]. This supports the relevance of the intention-to-treat (ITT) populations of the bimekizumab trials for informing to the decision problem.

A2. PRIORITY QUESTION. It is stated in CS Table 1 that the company's decision problem relates to adults with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated, and that this aligns with recommendations in previous NICE technology appraisals regarding biologics for the treatment of plaque psoriasis. However, previous NICE recommendations do not include patients with moderate disease (CS Table 4), and it is stated in CS B.1.4.3 that the proposed positioning of bimekizumab is restricted to people with severe disease. Please clarify whether the company's decision problem does include people with moderate as well as severe disease.

UCB response:

Previous NICE technology appraisals regarding biologics for the treatment of plaque psoriasis have consistently identified moderate to severe psoriasis as the population of interest. All NICE final scopes have specified that the relevant population is patients with moderate to severe plaque psoriasis, and from secukinumab (TA350) onwards all FADs for biologics in psoriasis have been titled "for the treatment of moderate to severe plaque psoriasis."[16-27] This is despite the FADs for all biologics specifying use in either severe or very severe disease, as described in B.1.4.1 Table 3.

Furthermore, all company submissions from ustekinumab (TA180) onwards use the terminology "moderate to severe" to define the population in the decision problem table of their submission. Given that the positioning of bimekizumab is in line with the recommendations of these previous biologics, UCB has taken the same approach to our decision problem table (B.1.1. Table 1) for consistency, and to avoid the risk of an interpretation that the intended positioning of bimekizumab differed to that of these existing biologics.

In our company submission, in order to align with the NICE final scope and with precedent, the decision problem population was therefore specified as moderate to severe plaque psoriasis.

However, no definition of moderate psoriasis is provided in either the NICE or BAD guidelines,[28, 29] it is therefore anticipated that any NICE guidance for bimekizumab would align with the criteria set out in previous appraisals, namely for the treatment of adults with plaque psoriasis only when:

- The disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 and
- The disease has not responded to other systemic treatments, including ciclosporin, methotrexate and phototherapy, or these options are contraindicated or not tolerated.

A3. In Appendix D.2, please clarify what 'completion' and 'discontinuation' refer to - do these terms refer to completion/discontinuation of study treatment or the study itself?

UCB response:

In the patient disposition figures in Appendix D.2 (Figures 9–12), 'Discontinued' refers to patients who discontinued the study (and thus study treatment) for any reason during the respective period, including but not limited to adverse events, lack of efficacy, loss to follow up or withdrawal of consent.

In the same figures, 'Completed' refers to patients who remained in the study throughout the relevant trial period and moved onto the subsequent trial period without discontinuing the study.

Pivotal phase III bimekizumab trials

A4. Table 16 in Appendix D.3 states that "study participants received placebo injections at certain visits in order to maintain the blind".

- For BE-VIVID, please confirm whether this means that patients randomised to ustekinumab arms were also given placebo injections every 4 weeks to maintain the blinding.
- In BE-SURE, were the initial and Q2W adalimumab doses masked by giving placebo injections to patients at corresponding timepoints in the other trial arms?
- In BE-RADIANT were the initial weekly secukinumab doses masked by giving patients placebo injections at the corresponding time points in the other trial arms?
- Similarly, in BE-READY, BE-SURE and BE-RADIANT, please confirm that patients allocated to bimekizumab Q8W also received placebo injections every 4 weeks?

UCB response:

Across all four trials, patients were given placebo injections to mimic the comparator with the most frequent dose regimen in order to maintain the treatment blinding. Placebo injections were given in all of the cases indicated in the question from the ERG. Additional placebo injections were also given to maintain the blind for the 45 mg and 90 mg doses of ustekinumab in BE VIVID, administered as one or two 45 mg subcutaneous injections, respectively.

A full summary of the dose and placebo schedules across treatment arms in the clinical trials is presented in Table 1.

Table 1: Dose and placebo schedules across treatment arms in the clinical trials

Trial	Initial Treatment Period (Week 0 to Week 16)	Maintenance Period (Week 16 onwards)
BE READY	Two injections Q4W: • Bimekizumab 320 mg: 2 x 160 mg bimekizumab injections Q4W • Placebo: 2 x placebo injections Q4W to maintain the blind	Two injections Q4W: • Bimekizumab 320 mg Q4W: 2 x 160 mg bimekizumab injections Q4W • Bimekizumab 320 mg Q8W: 2 x 160 mg bimekizumab injections Q8W, with 2 x placebo injections in the intervening fourth weeks to maintain the blind • Placebo: 2 x placebo injections Q4W to maintain the blind
BE VIVID	Two injections Q4W: • Bimekizumab 320 mg: 2 x 160 mg bimekizumab injections Q4W • Placebo: 2 x placebo injections Q4W to maintain the blind • Ustekinumab 45 mg: 1 x 45 mg ustekinumab injection and 1 x placebo injection at Week 0 and 4, followed by 2 x placebo injections at Weeks 8 and 12 to maintain the blind • Ustekinumab 90 mg: 2 x 45 mg ustekinumab injections at Week 0 and 4, followed by 2 x placebo injections at Weeks 8 and 12 to maintain the blind	Two injections Q4W: • Bimekizumab 320 mg: 2 x 160 mg bimekizumab injections Q4W • Ustekinumab 45 mg: 1 x 45 mg ustekinumab injection and 1 x placebo injection Q12W, with 2 x placebo injections in the intervening fourth weeks to maintain the blind • Ustekinumab 90 mg: 2 x 45 mg ustekinumab injections Q12W, with 2 x placebo injections in the intervening fourth weeks to maintain the blind
BE SURE	Two injections Q4W starting from Week 0, and two injections Q2W starting from Week 1: • Bimekizumab 320 mg: 2 x 160 mg bimekizumab injections Q4W, with 1 x placebo injection Q2W starting from Week 1 to maintain the blind • Adalimumab 40 mg: 2 x 40 mg adalimumab injections at Week 0, 1 x 40 mg adalimumab injection Q2W starting from Week 1, with 2 x placebo injections Q4W starting from Week 4 to maintain the blind	Two injections Q4W starting from Week 20, and two injections Q2W starting from Week 17: • Bimekizumab 320 mg Q4W: 2 x 160 mg bimekizumab injections Q4W, with 1 x placebo injection Q2W starting from Week 17 until Week 23 to maintain the blind • Bimekizumab 320 mg Q8W: 2 x 160 mg bimekizumab injections Q8W, with 2 x placebo injections in the intervening fourth weeks and 1 x placebo injection Q2W starting from Week 17 until Week 23 to maintain the blind • Adalimumab 40 mg: 1 x 40 mg adalimumab injection Q2W starting from Week 17 until Week 23, with 2 x placebo injections Q4W starting from Week 20 to maintain the blind. Switch to bimekizumab 320mg Q4W regimen starting at Week 24, with 2x

		160 mg bimekizumab injections Q4W.
BE RADIANT	Two injections Q4W starting from Week 0, and two injections at Weeks 1, 2 and 3: • Bimekizumab 320 mg: 2 x 160 mg bimekizumab injections Q4W, with 2 x placebo injections at Weeks 1, 2 and 3 to maintain the blind • Secukinumab 300 mg: 2 x 150 mg secukinumab injections at Weeks 1, 2 and 3, and Q4W starting from Week 4	Two injections Q4W: • Bimekizumab 320 mg Q4W: 2 x 160 mg bimekizumab injections Q4W • Bimekizumab 320 mg Q8W: 2 x 160 mg bimekizumab injections Q8W, with 2 x placebo injections in the intervening fourth weeks to maintain the blind • Secukinumab 300 mg: 2 x 150 mg secukinumab injections Q4W

Footnotes: All injections were administered subcutaneously.
Abbreviations: Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; Q12W: every 12 weeks.

A5. The CS Table 13 describes sensitivity analyses using different imputation methods for missing outcome data. Please provide a summary of the results of these sensitivity analyses or provide a description of how these results compared to the primary analyses.

UCB Response:

The approaches listed below were used in the bimekizumab Phase III clinical trials for handling missing data, as appropriate:

- Non-responder imputation (NRI) – Study participants who had missing data at the time point of interest were treated as though they did not respond to the treatment.
- Multiple imputation (MI) – Markov Chain Monte Carlo (MCMC)/Monotone Regression: Using MI methodology, intermittent missing data were imputed based on the MCMC method, and monotone missing data were imputed using monotone regression.
- Multiple Imputation – MCMC/Reference-based imputation: Using MI methodology, intermittent missing data were imputed based on the MCMC method, and monotone missing data were imputed using an imputation model based on placebo (reference) data.
- Last observation carried forward (LOCF): Post-baseline missing data were imputed by carrying forward the last available observation (including baseline).
- Observed case (OC): Missing data were not imputed. Only study participants with available data who had not discontinued study treatment at the given time point were considered.

NRI was used as the missing data assumption in the main analysis for all primary outcomes across the clinical trials, with MI (MCMC/monotone or referenced-based), OC, and LOCF applied in the sensitivity analyses. Across the four bimekizumab Phase III trials, the [redacted]

[redacted]

NRI was used in the main analysis for binary secondary outcomes and MI (MCMC/Monotone regression) in the main analysis for continuous data, with OC applied in the sensitivity analysis in both cases.

[redacted]

A6. Please clarify how the odds ratios have been calculated for the subgroup analyses presented in Appendix E?

UCB Response:

The odds ratios for the subgroup analyses presented in Appendix E are calculated using the stratified Cochran-Mantel-Haenszel (CMH) test where region and prior biologic exposure (yes/no) are used as stratification variables. Region and prior biologic exposure were selected as stratification variables in these analyses because they were stratification variables in the study randomisation and may have an impact on efficacy.

A7. The submission reports that the results of the phase III BE BRIGHT study are not available currently. Please indicate the timeframe for availability of the results.

UCB Response:

Interim results for BE BRIGHT are now available, covering additional safety and efficacy outcomes from the June 2020 interim data lock. Considering both the safety and efficacy results, a positive benefit-risk ratio for open-label bimekizumab was observed in participants with psoriasis in BE BRIGHT following up to 1 year of bimekizumab treatment in the feeder studies. The safety profile was consistent with the mechanism of action of bimekizumab and the population under investigation. Final results from BE BRIGHT are expected in mid-2023. Interim results from this open label study can be provided on request.

Network meta-analysis

A8a. Please describe how the risk of bias assessments for the pivotal trials and trials included in the NMA were conducted – how many reviewers performed the

assessments (e.g. two independent reviewers for each study) and how conflicts were resolved?

UCB Response:

Risk of bias assessment the four bimekizumab Phase III clinical trials (BE READY, BE VIVID, BE SURE and BE RADIANT) was completed according to the criteria outlined in the template for the NICE FTA company evidence submission. For each trial risk of bias was assessed by a single reviewer and validated for accuracy by a second reviewer. Any conflicts were resolved by discussion or, where necessary, by a third independent reviewer.

For the remaining trials included in the NMA, risk of bias assessment was conducted independently by one reviewer using the Cochrane Collaboration's Risk of Bias Assessment Tool (RoB 2) and validated by a second reviewer. A third reviewer was consulted to resolve disagreements, as necessary.

A8b. We note that a different set of quality criteria were used to assess the quality of the bimekizumab phase III trials compared to the risk of bias criteria used to assess the studies included in the network meta-analysis. Please elaborate on the origin/provenance of the latter set of criteria, and comment on whether/how the criteria assess two key dimensions of bias - allocation concealment and blinding.

UCB Response:

For each of the trials included in the NMA, other than the bimekizumab Phase III trials, the risk of bias was evaluated using the revised Cochrane Collaboration's Risk of Bias Assessment Tool (RoB 2).[30] This tool covers five domains as outlined in Table 2, of which 'bias arising from the randomisation process' and 'bias due to deviations from intended interventions' cover allocation concealment and blinding, respectively. For each domain, an algorithm is used to map responses to signalling questions to a proposed risk-of-bias judgment: "low risk of bias," "some concerns," or "high risk of bias". The results of the assessment of trials with RoB 2.0 are presented in Appendix D.1.7 Table 12.

Table 2: Overview of the Cochrane Collaboration's RoB 2 tool for assessing risk of bias

Bias domain	Signalling questions	Response options		
		Lower risk of bias	Higher risk of bias	Other
Bias arising from the randomisation process	1.1 Was the allocation sequence random?	Y/PY	N/PN	NI
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y/PY	N/PN	NI
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	N/PN	Y/PY	NI
Bias due to deviations	2.1 Were participants aware of their assigned intervention during the trial?	N/PN	Y/PY	NI

from intended interventions	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N/PN	Y/PY	NI
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	N/PN	Y/PY	NA/NI
	2.4 If Y/PY/NI to 2.3: Were these deviations likely to have affected the outcome?	N/PN	Y/PY	NA/NI
	2.5 If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	Y/PY	N/PN	NA/NI
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y/PY	N/PN	NI
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	N/PN	Y/PY	NA/NI
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Y/PY	N/PN	NI
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Y/PY	N/PN	NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N/PN	Y/PY	NA/NI
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	N/PN	Y/PY	NA/NI
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N/PN	Y/PY	NI
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N/PN	Y/PY	NI
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N/PN	Y/PY	NI
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N/PN	Y/PY	NA/NI
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	N/PN	Y/PY	NA/NI
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalised before unblinded outcome data were available for analysis?	Y/PY	N/PN	NI
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (eg, scales, definitions, time points) within the outcome domain?	N/PN	Y/PY	NI
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N/PN	Y/PY	NI

Source: Reproduced from Sterne et al. 2019[30]
Abbreviations: N: no; NA: not applicable; NI: no information; PN: probably no; PY: probably yes; Y: yes

Footnotes: Cells highlighted in blue indicate signalling questions relating specifically to allocation concealment and blinding.

A9. PRIORITY QUESTION. We note the statement: "An indirect treatment comparison in the ITT population was considered reasonable as characteristics such as outcome definitions, timepoints and analysis populations were fairly consistent across trials of treatments identified by the SLR" (Document B, page 89). Please summarise any evidence/clinical consensus on treatment effect modifiers in psoriasis, and describe the distribution of any such effect modifiers across the included NMA trials (in relation to potential clinical heterogeneity).

UCB Response:

To our knowledge, there is currently no clinical consensus on established treatment effect modifiers in plaque psoriasis. Although, prior exposure to biologic therapy has previously been hypothesised to be a treatment effect modifier in psoriasis,[31] in subgroup analyses of prior biologic exposure across the bimekizumab trials BE READY and BE VIVID (Pool E1) no interaction was observed (see Appendix E; Figures 16–18). Across the studies included in the NMA, the proportion of patients with prior exposure to biologic therapy ranged from 0% to 39.1%. In the absence of evidence to suggest that the efficacy of bimekizumab varies according to prior treatment, prior biologic treatment is assumed not to be a treatment effect modifier in the company submission.

Heterogeneity between studies may give rise to differences in baseline/placebo response rates that can represent a confounding factor in estimating true relative treatment effects. Adjustment for placebo response rate may therefore help to account for the impact of this heterogeneity to some extent. Adjustment for placebo response rate to take into account baseline risk has emerged as a common approach in recent plaque psoriasis NMAs and NICE guidelines recommend inclusion of a component for baseline risk, as relative effects of drugs in autoimmune diseases are often dependent on baseline risk (i.e. the placebo response rate and the relative efficacy of a treatment versus placebo are likely related).[37-39]

Given prior research and expert agreement, a baseline risk model was therefore assumed to be the most clinically valid; it was therefore decided *a priori* that, barring convincing evidence to the contrary, the base-case model for the company submission should include a parameter for baseline risk. Across the studies included in the NMA presented in the company submission, the PASI response rate for the placebo treatment arm at Weeks 10–16 ranged from 0–33.3% for PASI 50, 0–18.9% for PASI 75, 0–11.3% for PASI 90, and 0–2.0% for PASI 100.

A10. The submission states that "It should be noted that the results of the NMA presented in this submission and that of the NMA conducted for TA596 would not be expected to necessarily be the same, given that the NMA presented here includes a number of additional studies published since NICE appraisal TA596 was conducted". Apart from the pivotal phase III trials of bimekizumab, please cite or briefly

summarise the key characteristics of other additional studies published since TA596 (e.g. intervention and comparator).

UCB Response:

Table 3 presents a summary of the key characteristics of studies included in the NMA presented in this submission that were not included in the TA596 NMA (risankizumab). The company submission for TA596 is dated December 2018, although the exact date of the SLR searches is unclear.

For studies published prior to 2018, all additional studies included in the NMA presented in the bimekizumab submission that were not included in the TA596 NMA were those that included a comparator that was included in the bimekizumab submission's NMA for comprehensiveness but were not included in the TA596 NMA (highlighted in blue in the table below). For studies published in or after 2018, these studies may not have been included in TA596 as it is possible that they were published after the SLR informing the risankizumab NMA was conducted.

Table 3: Summary of key characteristics of studies included in NMA presented in this submission that were not included in the TA596 NMA (risankizumab)

Study	Primary endpoint (weeks)	Severity definition	Intervention and comparators	Mean age, years (SD)	Male, %	Disease duration, years	Percent with prior therapy, Biologic/non-biologic
Meffert, 1997[40] (NR)	10	PASI 8-25	Cyclosporin A 2.5 mg/kg/day	NR	NR	NR	NR/NR
			Placebo	NR	NR	NR	NR/NR
Heydendael, 2003[41] (NR)	16	PASI ≥8	Methotrexate 15mg QD for 4W then up to 22.5mg QD	41.6 (13)	65.1	NR	NR/NR
			Cyclosporine 3 to 5 mg/kg/day	38.3 (12.4)	69	NR	NR/NR
Barker, 2011[42] RESTORE 1 (Phase III)	16	PASI ≥12 BSA ≥10%	Infliximab 5 mg/kg Q8W	44.1	67	18.8	8.3/61.1
			Methotrexate 15 mg QW	41.9	69	17	8.4/64.7
Flytstrom, 2008[43] (NR)	12	NR	Methotrexate 7.5–15 mg QW	48	75.7	NR	NR/NR
			Ciclosporin 3–5 mg/kg QD	45	87.1	NR	NR/NR
Gisondi, 2008[44] (NR)	24	NR	Etanercept 25 mg BIW	55.3 (10.9)	54.6	23.5	0/NR
			Acitretin 0.4 mg/kg QD	55 (11.3)	60	18.8	0/NR
Caproni, 2009[45] (NR)	12	PASI ≥10 BSA ≥10%	Etanercept 50 mg BIW	28-67	43.3	NR	NR/NR
			Acitretin 0.4 mg/kg/day	31-65	36.7	NR	NR/NR
Antiga, 2010[46] (NR)	12	PASI ≥10 BSA ≥10%	Etanercept 50 mg BIW	31-63	40	NR	NR/NR
			Acitretin 0.4 mg/kg/day	27-58	50	NR	NR/NR
Gottlieb, 2011[47] (Phase III)	12	PASI ≥12 BSA ≥10% PGA ≥3	Etanercept 50 mg BIW	43.1 (12.5)	69.5	17	14.2/NR
			Placebo	44 (13.6)	69.1	19.1	14.7/NR
Reich, 2012[48] (Phase II)	12	PASI ≥12 BSA ≥10%	Certolizumab pegol 200 mg Q2W	43.3 (10.1)	75	21	22/NR

Study	Primary endpoint (weeks)	Severity definition	Intervention and comparators	Mean age, years (SD)	Male, %	Disease duration, years	Percent with prior therapy, Biologic/non-biologic
			Certolizumab pegol 400 mg Q2W	43.6 (12.4)	72	19.6	24/NR
			Placebo	43.3 (12.8)	63	19.7	24/NR
Rich, 2013[49] (Phase II)	12	NR	Secukinumab 150 mg Q4W	44.2 (13.0)	75.4	16.9	29.7/NR
			Placebo	44.2 (12.6)	65.7	15.4	25.4/NR
Papp, 2015[50] (Phase II)	16	PASI ≥12 BSA ≥10%	Tildrakizumab 100 mg Q12W	45.5 (12.8)	85	NR	0*/NR
			Tildrakizumab 200 mg Q12W	43.2 (12.6)	76	NR	0*/NR
			Placebo	45.9 (11.7)	83	NR	NR/NR
Bachelez, 2015[51] (Phase III)	12	PASI ≥12 BSA ≥10%	Etanercept 50 mg BIW	42	70	18	11/NR
			Placebo	46	66	17	11/NR
Goldminz, 2015[52] (NR)	16	PGA≥3	Adalimumab 40 mg Q2W	50.5 (NR)	73.3	17.3	0/40
			Methotrexate 7.5-25 mg/week	50.3 (NR)	86.7	21.5	0/26.7
Gordon, 2017[53] (Phase III)	12	NR	Placebo	NR	NR	NR	NR/NR
			Etanercept 25 mg BIW				
			Etanercept 50 mg BIW				
			Placebo				
de Vries, 2017[54] PIECE (NR)	24	PASI ≥10 and/or BSA ≥ 10 and/or PASI≥ 8 Skindex-29 score ≥35	Etanercept 50 mg BIW	42.4 (13.2)	56	17.9	NR/NR
			Infliximab 5 mg/kg Q8W	45.9 (13.9)	72	21.5	NR/NR
Reich, 2017[42]	12	PASI ≥12	Tildrakizumab 200 mg Q12W	46.9 (13.2)	73	NR	23/NR

Study	Primary endpoint (weeks)	Severity definition	Intervention and comparators	Mean age, years (SD)	Male, %	Disease duration, years	Percent with prior therapy, Biologic/non-biologic
RESURFACE 1 (Phase III)		BSA ≥10% PGA ≥3	Tildrakizumab 100 mg Q12W	46.4 (13.3)	67	NR	23/NR
			Placebo	47.9 (13.5)	65	NR	23/NR
Reich, 2017[42] RESURFACE 2 (Phase III)	12	PASI ≥12 BSA ≥10% PGA ≥3	Tildrakizumab 200 mg Q12W	44.6 (13.6)	72	NR	12/NR
			Tildrakizumab 100 mg Q12W	44.6 (13.6)	72	NR	13/NR
			Etanercept 50 mg BIW	45.8 (14)	71	NR	12/NR
			Placebo	46.4 (12.2)	72	NR	13/NR
Lebwohl, 2018[55] CIMPACT (Phase III)	12	PASI ≥12 BSA ≥10% PGA ≥3	Certolizumab pegol 200 mg Q2W	46.7 (13.5)	68.5	19.5	26.7/NR
			Certolizumab pegol 400 mg Q2W	45.4 (12.4)	64.1	17.8	28.7/NR
			Etanercept 50 mg BIW	44.6 (14.1)	74.7	17.4	30/NR
			Placebo	46.5 (12.5)	59.6	18.9	19.3/NR
Gottlieb, 2018[56] CIMPASI-I (Phase III)	16	PASI ≥12 BSA ≥10% PGA ≥3	Certolizumab pegol 200 mg Q2W	44.5 (13.1)	70.5	16.6	31.6/69.5
			Certolizumab pegol 400 mg Q2W	43.6 (12.1)	68.2	18.4	33/69.3
			Placebo	47.9 (12.8)	68.6	18.5	29.4/70.6
Gottlieb, 2018[56] CIMPASI-II (Phase III)	16	PASI ≥12 BSA ≥10% PGA ≥3	Certolizumab pegol 200 mg Q2W	46.7 (13.3)	63.7	18.8	35.2/71.4
			Certolizumab pegol 400 mg Q2W	46.4 (13.5)	49.4	18.6	34.5/72.4
			Placebo	43.3 (14.5)	53.1	15.4	28.6/73.5
Stein, 2018[57] UNVEIL (Phase IV)	16	BSA 5%–10% sPGA=3	Apremilast 30 mg BID	48.6 (15.4)	50	17.5	0/NR
			Placebo	51.1 (13.7)	56.2	13.9	0/NR

Study	Primary endpoint (weeks)	Severity definition	Intervention and comparators	Mean age, years (SD)	Male, %	Disease duration, years	Percent with prior therapy, Biologic/non-biologic
Gefland, 2018[58] VIP (Phase IV)	12	PASI ≥12 BSA ≥10	Adalimumab 40 mg Q2W	44.1 (14)	72.7	14.9	NR/NR
			Placebo	44.3 (14.5)	64.5	19.3	NR/NR
Reich, 2019[59] ECLIPSE (Phase III)	12	NR	Guselkumab 100 mg Q8W	NR	NR	NR	NR/NR
			Secukinumab 300 mg Q4W	NR	NR	NR	NR/NR
			Guselkumab 100 mg Q8W	NR	NR	NR	NR/NR
			Secukinumab 300 mg Q4W	NR	NR	NR	NR/NR
von Stebut, 2019[60] CARIMA (Phase III)	12	PASI ≥10	Secukinumab 150 mg	46 (14.4)	57.4	20.8	31.1/89.6
			Secukinumab 300 mg	44.2 (12.9)	77.1	20.6	37/85.2
			Placebo to Secukinumab 150 mg ‡	46.8 (13.1)	69.6	20.3	39.1/69.6
			Placebo Secukinumab 300 mg ‡	43.7 (11.4)	69.2	18.9	30.8/92.3
Reich, 2019[61] TRANSFIGURE (Phase III)	16	PASI ≥12 BSA ≥10% NAPSI ≥16 at least 4 fingernails	Secukinumab 300 mg Q4W	45.1 (12.9)	80	18	24/NR
			Secukinumab 150 mg Q4W	43.5 (10.9)	82	20	22/NR
			Placebo	43.6 (11.2)	80	17.4	23/NR
Ohtsuki, 2019[62] SustaIMM (Phase II/III)	16	PASI ≥12 BSA ≥10% sPGA ≥3	Risankizumab 75 mg W0 and 4 then Q12W	51.5 (12.3)	83	NR	14
			Risankizumab 150 mg W0 and 4 then Q12W	53.3 (11.9)	91	NR	29
			Placebo	50.9 (11.2)	78	NR	24
Krueger, 2019[63] CAIN457A2223 (Phase II)	12	PASI ≥12 BSA ≥10% mIGA 2011 ≥3	Secukinumab 300 mg W0, 1, 2, 3, 4 then Q4W	47.5 (14)	71	NR	NR
			Placebo	50.3 (13.8)	50	NR	NR

Study	Primary endpoint (weeks)	Severity definition	Intervention and comparators	Mean age, years (SD)	Male, %	Disease duration, years	Percent with prior therapy, Biologic/non-biologic
Warren, 2020[64] IMMerge (Phase III)	16	PASI ≥12 BSA ≥10% sPGA ≥3	Risankizumab 150 mg W1, 4, then Q12W	47.3 (13.4)	68.3	18.6	37.8
			Secukinumab 300 mg W0, 1, 2, 3, 4 then Q4W	46.8 (14.9)	62	17.4	35.6
Gelfand, 2020[65] VIP-S (NR)	12	PASI ≥12 BSA ≥10% mIGA 2011 ≥3	Secukinumab 300 mg W0, 1, 2, 3, 4 then Q4W	47.9 (12.7)	71.7	16.3	43.5
			Placebo	47 (14.7)	62.2	15.4	35.6

Footnotes: Cells highlighted in blue indicate comparators that were included in the bimekizumab submission NMA but not in the risankizumab submission NMA.
Abbreviations: BID: twice daily; BIW: twice weekly; BSA: body surface area; mIGA: modified Investigator's Global Assessment; NAPSI: Nail Psoriasis Severity Index; NR: not reported; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation; sPGA: static Physician's Global Assessment; W: Week.

A11. PRIORITY QUESTION. Please provide the rationale for the development of the REZ model and the relaxation of the proportional treatment effects assumption. Is there any real-world evidence that the proportional treatment effects assumption is violated?

UCB Response:

The proportional treatments effects assumption represents a useful assumption that can support the conduct of NMA in the absence of availability of comprehensive data across the ordered categorical variables. The NICE Decision Support Unit Technical Support Document 2 states, by way of example: "Trials may report ACR-20, ACR-50 and ACR70, or only one or two of these end-points. We can provide a coherent model and make efficient use of such data by assuming that the treatment effect is the same regardless of the cut-off. This assumption can be checked informally by examining the relative treatment effects at different cut-offs in each trial and seeing if they are approximately the same".[66] This summarises the value of a proportional treatment effects assumption in allowing a coherent model in the absence of complete data, provided the underlying assumption of proportional treatment effects is supported.

However, this does not mean that the proportional treatment effects assumption is absolutely necessary or indeed *a priori* the most appropriate approach, particularly where there is comprehensive reporting of the relevant outcome data. Incorporating the proportional treatment effects assumption requires that this assumption is justified, whereas the REZ model requires weaker/fewer assumptions about the structure of the data.

Given this, we consider that the standard model that includes a proportional treatment effect assumption should not automatically be the default in a context where there is a large volume of data across trials, including PASI outcomes that are well and consistently reported across those trials. In this context, the company perspective was that model selection should instead be made on the basis of best fit. The model fit of the REZ model was found to be superior, providing support that it is a better model for the data and implying that the proportional hazards assumption is at some level violated. Furthermore, previously published (frequentist binomial) NMAs have found the ranking of the treatments to differ between the PASI 75, PASI 90 and PASI 100, suggesting that the relaxation of the assumption of proportional treatment effects is appropriate.[67-69]

A12. PRIORITY QUESTION. Please provide the trial data used in the WinBUGS REZ model, together with an explanation of any imputation. Please provide the data as formatted for running with the WinBUGS code.

UCB Response:

The files for the base case (REZ-adjusted-random effects) analysis are provided in the reference pack accompanying this response (file names prefixed 'A12'):

- Bayesian model code (…_modelJAGS.txt)
- Data files (…_dataJAGS.txt)

- Initials files (…_initsJAGS.RData; …inits1.txt)

These documents can be directly fed to the “jags” function of the R package called “R2jags”. The R data file includes the initials for 3-chain analysis.

In addition to the inclusion of the text/RData files in the reference pack as noted above, the Bayesian model code and input data text files are also copied in the appendix to this response document. The text file corresponding to the initials of MCMC chain 1 from the _’initsJAGS.RData’ file is also included in the appendix. Initials for chain 2 and 3 were in exactly in the same format, but sufficiently varied.

To help with understanding the model code, please note that the model code file uses the following terminology to define the associated parameters:

- “dd” (basic effects parameters)
- “BetaPlac” (beta-coefficient of the baseline/placebo risk)
- "sd" (the between-study standard deviation)
- "Pbitdiff" (probit difference at the lowest PASI cut-off, ie PASI50)
- "Pbitdiffprob" (probability of treatment better than comparator)
- "Thresh" (response probabilities in [PASI level, treatment id] format)
- "sdz" (standard deviation of z parameter)
- "totresdev" (residual deviance)

Additionally, please see in the appendix to this response document a library of the treatment IDs in the model.

We did not impute any data or any parameter in the REZ model; as the REZ model is an enhancement of the standard multinomial model, the same approach as would be used for the standard multinomial model was followed, and PASI data was used as reported without imputation.

A13. PRIORITY QUESTION. Please provide the WinBUGS code used for the standard multinomial probit random effects model.

UCB Response:

The files for the standard unadjusted random-effect probit model analysis are provided in the reference pack accompanying this response (file names prefixed ‘A13’):

- Bayesian model code (…_modelJAGS.txt)
- Data files (…_dataJAGS.txt)
- Initials files (…_initsJAGS.RData)

These documents can be directly fed into the “jags” function of the R package called “R2jags”. The R data file includes the initials for the 3-chain analysis.

To help with understanding the model code, please note that the model code file uses the following terminology to define the associated parameters:

- "dd" (basic effect parameters with indices on posttreat ids), which is the same as the parameter "d" with indices as pretreat IDs (the treatment IDs are provided in the 'library of treatment IDs' in the Appendix to this response)
- "sd" (the between-study standard deviation)
- "Pbitdiff" (probit difference at the lowest PASI cut-off, i.e. PASI 50)
- "Pbitdiffprob" (probability of treatment better than comparator)
- "Thresh" (response probabilities in [PASI level, treatment id] format)
- "totresdev" (residual deviance)

A14. PRIORITY QUESTION. Please clarify whether the baseline risk model was run for PASI-75 (as suggested by Figure 2, Appendix D) or PASI-50 as suggested by Appendix D.1.5. Please provide (i) the results for the baseline risk model, (ii) the WinBUGS code used for the baseline risk model, and (iii) the data used in the model, together with an explanation of any imputation.

Analyses of both PASI 50 and PASI 75 were conducted, with models including a component for baseline risk. A continuity correction proportional to the arm size was applied to the PASI 75 data (adding correction to the responders and 2 times correction to the arm sizes) in trials whenever a treatment arm (always placebo) had 0 events. No imputation was required or performed.

Please find the requested results in Figure 1 and Figure 2; the requested files are provided in the reference pack (file names prefixed 'A14').

Figure 1: Forest plot of odds ratios of achieving at least a PASI 50 response at 10–16 weeks for bimekizumab vs each treatment included in the NMA, baseline risk model

Abbreviations: CrI: credible interval; NMA: network meta-analysis; PASI: psoriasis area and severity index.

Figure 2: Forest plot of odds ratios of achieving at least a PASI 75 response at 10–16 weeks for bimekizumab vs each treatment included in the NMA, baseline risk model

Abbreviations: CrI: credible interval; NMA: network meta-analysis; PASI: psoriasis area and severity index.

A15. Please provide methods and results of the assessment of inconsistency in each of the NMA models.

UBC Response:

Due to the additional time required to address this request, we plan to provide a response to this question by 5th March 2021. It should be noted that the evidence base used in the NMA is consistent with previous psoriasis submissions to NICE, as are the estimates of PASI response.

A16. Was any consideration given to conducting an NMA for the maintenance period of the trials, in addition to the initial (induction) treatment period? How might this inform the NICE appraisal committee's decision making, in the company's opinion?

UCB Response:

It is not anticipated that an NMA for the maintenance period of the trials would impact the NICE appraisal committee's decision-making for the following reasons:

1. Many clinical trials in plaque psoriasis involve crossover or re-randomisation of patients after the initial treatment period. This means that there is limited placebo data available for the maintenance treatment period and in some trials maintenance data for specific interventions are available only for 'responders', with the definition of a response varying across trials. The number of trials that can be included in the network would therefore be

limited and the analysis may require a number of assumptions. As such, any conclusions from such an NMA would be less reliable than those drawn from an NMA assessing the initial treatment period and would not be a strong basis for decision-making.

2. The only efficacy input included in the economic model for the current submission is the PASI 75 response rate at Week 16, with the assumption that treatment response is then maintained at this same level from Week 16 onwards. This approach is aligned with the precedent in plaque psoriasis, with all prior biologic submissions incorporating this same assumption in their economic modelling. An NMA for the maintenance treatment period would therefore not be expected to have an impact on the conclusions of the economic modelling.

3. To our knowledge, previous submissions for biologics in plaque psoriasis have also not included an NMA for the maintenance treatment period. Prior decisions made by NICE appraisal committees regarding biologics for psoriasis treatment have therefore been focused upon relative effectiveness response data derived from the initial treatment period.

In summary, an NMA of the maintenance period is likely to be limited in nature due to the structure of plaque psoriasis clinical trials and, were such an NMA to be conducted in spite of these data challenges, prior precedent suggests that it would not be expected to play an important role in NICE decision-making.

A17. Please consider repeating the NMA for the DLQI outcome. The DLQI and PSAI address complimentary aspects of psoriasis and an indirect comparison of bimekizumab with existing treatments on both of these measures may provide a more comprehensive assessment of efficacy.

UCB Response:

An NMA for the DLQI outcome has previously been considered for this submission. However, this NMA was deprioritised for the following reasons:

1. The only efficacy inputs that have been used to directly inform the economic modelling in prior biologic appraisals are PASI response rates, specifically PASI 75 response rates in the case of the cost-comparison approach. Priority was therefore given to extracting PASI data over DLQI, given the constrained timelines following the completion of the systematic literature review and the more recent read out of the data from the BE RADIANT trial.

2. An NMA for the DLQI outcome would not be expected to have a material impact on the NICE appraisal committee's decision-making. To our knowledge, DLQI NMAs have rarely been undertaken, with only two prior psoriasis appraisals conducting these analyses in the past.[1, 14] Where NMAs for DLQI have been provided in prior appraisals, it does not appear that they have been used to inform conclusions about therapeutic equivalence; in both TA596 (risankizumab) and TA521 (guselkumab), the lack of discussion around these analyses in both the company submissions and the subsequent guidance indicate that the results of the DLQI NMAs were unlikely to have been key drivers of the ultimate decision.

Based on the evidence that is visible to UCB, the prior psoriasis appraisals (including those that undertook DLQI NMAs) all presented direct evidence from their Phase 3 studies as the primary evidence to support comparisons of relative treatment effects on DLQI. To ensure data is accurately extracted and analyses conducted appropriately, an NMA for the DLQI outcome would take several weeks and is therefore not available for inclusion in this response. In the absence of a full DLQI NMA, UCB would like to highlight the DLQI data obtained in the four bimekizumab Phase III clinical trials, which demonstrate that the benefit of bimekizumab extends to the DLQI outcome. By Week 16, bimekizumab demonstrated greater DLQI response rates than all direct comparators (Document B, Figure 11):

- [redacted]
- [redacted]

A18. PRIORITY QUESTION. Please justify the choice of somewhat informative priors for the random effect standard deviation, Uniform(0,1), and square root SD around the probit thresholds, Uniform(0,0.5), rather than the traditional vague Uniform(0,5) in the REZ model. Also BetaPlac (baseline placebo effect on probit scale?) in the WinBUGS code (Figure 4, Appendix D) has a narrower Normal(0,100) than is traditionally accepted as vague. Please report the posterior estimates for each of these parameters.

UCB Response:

Choice of priors

The company considered that the choice of priors for RE standard deviation that were narrower than the 'traditional' vague priors to be reasonable and unlikely to adversely affected the estimation of relative effectiveness in the company submission, based on the following rationale:

1. The 'traditional' vague priors, including some of those that are provided in some NICE exemplar code,[66] posit a mean and distribution of potential RE variation that is far greater than would exist in real data. Lambert et al. (2005) demonstrated that if a selected distribution for a vague/non-informative prior is too wide, this can affect the estimation of variances, due to the role of the prior in estimating an effect.[70]

2. Whilst empirical priors were not used, priors published in the literature were much less vague than that implied by U[0,5] in the bimekizumab NMA.[71, 72]

3. The starting assumption for the variances was substantially higher than the variances seen in the data. A prior of [0,5] essentially assumes that the average estimate for the standard deviation of the RE variance is 2.5; this is substantially greater than that observed in the data (approximately 0.11).

Regarding the choice of prior selected for the slope for baseline risk, although this may be narrower than the threshold traditionally accepted as vague, the Normal (0,100) prior is

considered reasonable as a slope greater than 0 or less than –1 would be difficult to interpret; accordingly, the N(0,100) prior used is considered to be relatively uninformative.

Although the selected priors may be considered narrower than the 'traditional' vague priors, the large number of trials included in the NMA (n=84) meant that the impact of the selected priors on the observed results is minimal. Following receipt of these clarification questions, further exploration of the impact of prior selection on the model results has been conducted, finding extremely similar posterior estimates compared with using more vague priors (Table 4).

Table 4: The impact of prior selection on posterior estimates

Model (all random-effects)	SD prior	SDZ prior	BLbeta prior	BLbeta (95% CrI)	SDZ (95% CrI) posterior	SD (95% CrI) posterior	Dbar	DIC
REZ, adjusted	U(0,1)	U(0,0.5)	N(0,100)	-0.7134 (-1.0154, -0.5542)	0.1122 (0.0878, 0.1458)	0.1133 (0.0771, 0.1622)	706.83	961.33
REZ, adjusted	U(0,5)	U(0,5)	N(0,1000)	-0.7125 (-1.0122, -0.5494)	0.1122 (0.0878, 0.1453)	0.1129 (0.0772, 0.1612)	706.75	960.48
REZ, unadjusted	U(0,1)	U(0,0.5)	–	–	0.1135 (0.0885, 0.1469)	0.1110 (0.0640, 0.1634)	699.09	931.24
REZ, unadjusted	U(0,5)	U(0,5)	–	–	0.1135 (0.0891, 0.1474)	0.1113 (0.0620, 0.1627)	699.18	934.43
Standard, adjusted	U(0,1)	–	N(0,100)	-0.7215 (-1.0110, -0.5620)	–	0.1093 (0.0747, 0.1550)	949.48	1144.59
Standard, adjusted	U(0,5)	–	N(0,1000)	-0.7192 (-1.0066, -0.5672)	–	0.1090 (0.0756, 0.1543)	949.16	1143.52
Standard, unadjusted	U(0,1)	–	–	–	–	0.1146 (0.0667, 0.1660)	942.06	1118.74
Standard, unadjusted	U(0,5)	–	–	–	–	0.1126 (0.0645, 0.1644)	942.62	1119.31

Abbreviations: BL: baseline; CrI: credible interval; DIC: deviance information criterion; SD: standard deviation; SDZ: standard deviation of the *z* variable.

A19. Please also explain the calculation of A ~ dnorm(0.919,268.744961031981) in the REZ model code (Figure 4, Appendix D). Is this the baseline risk on the probit scale?

UCB Response:

Yes, this is the baseline risk on the probit scale. This distribution was identified using a multinomial 'natural history' model, which considered studies with PASI 50 or PASI 75 placebo data; this analysis was limited to studies with sample sizes >50 participants and published from 2013 onwards, in order to generate a clinically relevant anchor, as it is likely that the efficacy of placebo (i.e. standard of care) has changed over time. The posterior distribution of the anchor, A, had mean = 0.919 and SD = 0.061 or precision = 1/0.0612 = 268.7449 in probit scale (the PASI 50 placebo response rate = 17.9%) and these estimates were imputed in all (fixed/random-effect, baseline risk adjusted/unadjusted, REZ/standard) probit models.

A20. PASI response outcomes from the NMA are presented in terms of absolute probabilities. Please could the company present PASI response as relative risks to facilitate comparisons with other NMAs.

UCB Response:

Odds ratios for achieving a PASI 75 at Week 10–16 with bimekizumab versus each comparator, and with each comparator versus placebo are presented in Table 5 for the base case NMA (baseline risk-adjusted, random effects, REZ).

Table 5: Odds ratios for achieving a PASI 75 response at Week 10–16

Comparator	Bimekizumab vs Comparator OR [95% CrI]	Comparator vs Placebo OR [95% CrI]
Placebo	[redacted]	[redacted]
Acitretin 0.4 mg/kg/day	[redacted]	[redacted]
Apremilast 30 mg	[redacted]	[redacted]
Methotrexate 7.5 to 25 mg	[redacted]	[redacted]
DMF up to 720 mg	[redacted]	[redacted]
Etanercept 25 mg	[redacted]	[redacted]
Cyclosporine 2.5 to 5 mg	[redacted]	[redacted]
Etanercept 50 mg	[redacted]	[redacted]
Tildrakizumab 100 mg	[redacted]	[redacted]
Tildrakizumab 200 mg	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]	[redacted]
Certolizumab pegol 200 mg	[redacted]	[redacted]
Ustekinumab 90 mg	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]
Ustekinumab 45 or 90 mg	[redacted]	[redacted]
Certolizumab pegol 400 mg	[redacted]	[redacted]
Infliximab 5 mg/kg	[redacted]	[redacted]

Secukinumab 300 mg	[redacted]	[redacted]
Guselkumab 100 mg	[redacted]	[redacted]
Brodalumab 210 mg	[redacted]	[redacted]
Risankizumab 150 mg	[redacted]	[redacted]
Ixekizumab 80 mg	[redacted]	[redacted]

Abbreviations: CrI: credible interval; DMF: dimethyl fumarate; OR: odds ratio; PASI: Psoriasis Area and Severity Index.

A21. Was a probit link considered as an alternative scenario to the binomial logit model for the safety endpoints?

UCB response:

We did not consider probit link as an alternative scenario to the binomial logit model for the safety endpoints as this comprised binary event data. Our understanding is that a probit model is generally considered for categorical nested data and we are not familiar with its use for binary efficacy data such as the presence/absence of serious adverse events.

Section B: Clarification on cost-comparison data

B1. PRIORITY QUESTION: CS Table 2 states that [redacted] **Please report the proportion of patients in the BE READY, BE VIVID, BE SURE and BE RADIANT trial populations** [redacted]**. Please also conduct a scenario analysis to estimate the impact on the costs of bimekizumab if all patients who met this criteria** [redacted]

UCB Response:

On Friday 19th February 2021, UCB sought further guidance from NICE and the ERG with regards to how to approach Question B1. As UCB has not received any further communication on this point, we have included the previously mentioned communication with NICE in our response pending further guidance from NICE and the ERG - please find this below for your reference.

Additional Information and Data Related to Question B1:

The [redacted].

[redacted]

Footnotes: The vertical line shows the time (Week 16) when the study participants in the second treatment group switch from 320mg Q4W regimen to 320mg Q8W regimen.
Abbreviations: 320mg Q4W, 320mg Q8W: 320mg Q4W followed by 320mg Q8W from Week 16 onwards; ADAb: anti-drug-antibody; PASI: Psoriasis Area and Severity Index; PASI 75: 75% improvement from baseline in PASI; PASI 90: 90% improvement from baseline in PASI; PASI 100: 100% improvement from baseline in PASI; Q4W: every 4 weeks; Q8W: every 8 weeks.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

UCB request for clarification from NICE/ERG to inform company response by 24th February:

Across NICE guidance for the treatment of plaque psoriasis, an adequate response is typically defined as **PASI 75**, with treatment continuation or discontinuation at the end of the initial treatment period being determined based on the achievement of a PASI 75 response.

[redacted] The bimekizumab cost comparison analysis submitted by UCB is therefore based on the proportion of patients treated with bimekizumab (and the respective comparators) that will achieve an adequate response as defined by PASI 75 and will thus continue to incur treatment costs based on a Q8W maintenance dose.

Unless NICE guidance for bimekizumab is expected to include language on posology options beyond week 16 for *PASI 75 responders*, then our understanding is that the additional analysis is beyond the scope of the decision problem. UCB would therefore request guidance from NICE and the ERG on:

- Whether they believe that the original analysis in the company submission is sufficiently aligned with the NICE decision problem to not warrant a further analysis in response to Question B1?
- If the request to model a proportion of patients receiving Q4W maintenance dosing per Question B1 continues to be pertinent to the decision problem, given the additional data and information shared above, UCB would welcome guidance from the ERG and NICE on how best to approach the analysis within the context of existing NICE guidance specifying PASI 75 as an adequate response, such that we can provide a suitable response to Question B1.

Section C: Textual clarification and additional points

C1. It is stated in B.4.2.1 that the population for the cost comparison is adult patients with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. This is not consistent with the proposed use of specified in CS section B.1.1.1, which is restricted to severe disease. Please clarify the target population for the cost-comparison.

UCB Response:

Please see our responses to questions A1 and A2 for discussion of the decision problem and the precedent regarding the use of the phrase ‘moderate to severe’ in prior plaque psoriasis appraisals. Ultimately the population that the cost comparison aims to address is in line with the NICE-recommended population for previous biologics in plaque psoriasis, namely patients with severe psoriasis as defined by NICE’s PASI and DLQI criteria who have not responded to, are contraindicated to, or are not able to tolerate non-biologic systemic treatments.

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Appendix

QUESTION A12

Model code (from reference: '…modelJAGs.txt')

```
###! REZ - baseline adjusted - Random effects model

model{
        #! *** PROGRAM STARTS

    dummyvar<-nclass[1]+posttreat[1]+poststudy[1]

    for(i in 1:85){
    #! LOOP THROUGH STUDIES

    w[i,1] <- 0
        #! adjustment for multi-arm trials for control arm

    delta[i,1] <- 0
    #! treatment effect is zero for control arm

    mu[i] ~ dnorm(0,0.001)
            #! vague priors for all trial baselines

    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

            r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j])
    #! binomial likelihood

            q[i,k,j] <- 1-(p[i,k,C[i,(j+1)]]/p[i,k,C[i,j]])                    #!
conditional probabilities

            theta[i,k,j] <- mu[i] + delta[i,k] + z[ntreat[i,k],C[i,(j+1)]-1] +
(BetaP[ntreat[i,k]]-BetaP[ntreat[i,1]]) * (mu[i]-Mmu)

            rhattreat[i,k,j] <- q[i,k,j] * n[i,k,j]                            #!
predicted number events

            dv[i,k,j] <- 2 * (r[i,k,j]*(log(r[i,k,j])-log(rhattreat[i,k,j]))   #!
Deviance contribution of each category

                        +(n[i,k,j]-r[i,k,j])*(log(n[i,k,j]-r[i,k,j]) - log(n[i,k,j]-
rhattreat[i,k,j])))
```

```
                }

            dev[i,k] <- sum(dv[i,k,(1:(nc[i]-1))])
            #! deviance contribution of each arm

            avgdev[i,k] <- dev[i,k]/(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]

            #p[i,k,C[i,j]] <- 1 - theta[i,k,j-1]
        #! link function

                phi.adj[i,k,j] <- step(8+theta[i,k,(j-1)]) * (step(theta[i,k,(j-1)]-8) + step(8-
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])

            md[i,k] <- dd[ntreat[i,k]] - dd[ntreat[i,1]] + sw[i,k]
            #! mean of LHR dist (with multi-arm trial correction)

            taud[i,k] <- prec*2*(k-1)/k
            #! prec of LHR dist (with multi-arm trial correction)

            w[i,k] <- (delta[i,k] - dd[ntreat[i,k]] + dd[ntreat[i,1]])
        #! adjustment, multi-arm RCTs

            sw[i,k] <- sum(w[i,(1:(k-1))])/(k-1)
            #! cumulative adjustment for multi-arm trials

        }

        resdev[i] <- sum(dev[i,1:na[i]])

        }

        totresdev <- sum(resdev[])
            #! Total Residual Deviance



        for (i in 1:23) {
```

```
            z[i,1] <- 0


            for (j in 2:(Cmax-1)) {


            z[i,j] <- z[i,(j-1)] + z.aux[i,j]
        #! ensures z[j]~Uniform(z[j-1], z[j-1]+5)

            z.aux[i,j] ~ dnorm(MeanZ[j],precz)

            }

        }


        for (j in 2:(Cmax-1)) {

            MeanZ[j] ~ dunif(0,5)

        }

        precz <-1/(sdz*sdz)

        sdz ~ dunif(0.001,0.5)


        ###calculate prob of achieving threshold- on treat k

        A ~ dnorm(0.919, 268.744961031981)


        for (k in 1:23) {

            for (j in 1: (Cmax-1)) { TThresh[j,k] <- 1 - phi(A + dd[k] + z[k,j] + (BetaP[k])*(A-
Mmu)) }

        }


        dd[1] <- 0
            #! treatment effect is zero for reference treatment

        BetaP[1]<- 0

        BetaPlac ~ dnorm(0,0.01)
            #! vague prior for baseline effect on probit values
```

```
for (k in 2:23){
        dd[k] ~ dnorm(0,0.001) #! vague priors for treatment effects
        BetaP[k]<-BetaPlac
}



sd ~ dunif(0.001,1)
        #! vague prior for between-trial SD
tau<-sd
prec<- pow(tau,-2)
        #! between-trial precision
tau2<-1/prec


for (index in 1:23){
        for (i in 1:(Cmax-1)) {
        Thresh[i,pretreat[index]]<-TThresh[i,index]
        }
        d[pretreat[index]]<-dd[index]
        rk[pretreat[index]]<-rkk[index]
        bestt[index]<-step(1.1 - rkk[index])
        for (j in 1:23) {
                preeffect[j,index]<- equals(index,rkk[j])
        }
}
```

rkk<- rank(dd[]) #Used when best = lowest, but 1-p is modeled in probit anlaysis, so higher dd[] is better is the event is good in probit analysis - change during post-precessing

```
	for (index in 1:85){
		study[prestudy[index]]<-mu[index]
	}

	###! All pairwise comparisons of differences in probit
	for (c in 1:(23-1)){
		for (k in (c+1):23){
			Pbitdiff[pretreat[c],pretreat[k]] <- dd[c] - dd[k]		#! direction of probit difference of all comparisons is changed here for ranking
			Pbitdiffprob[pretreat[c],pretreat[k]] <- step(Pbitdiff[pretreat[c],pretreat[k]])
			}
		}
}
```

Initials files (from reference: '…inits1.txt')

```
# 85 trials - length of mu; 23 treatments are compared in this network - length of dd
# following data were the initial values used for the first chain, initJAGS[[1]] in the R data file.
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,
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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)

dd <- c(NA, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)

sd <- 0.1

sdz <- 0.2

BetaPlac <- -0.2

z.aux <- structure(c(NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA,
NA, NA, NA, NA, NA, NA, NA, NA, NA, 0.2, 0.2, 0.2, 0.2, 0.2,
0.2, 0.2, 0.2, 0.2, 0.2, 0.2, 0.2, 0.2, 0.2, 0.2, 0.2, 0.2, 0.2, 0.2,
0.2, 0.2, 0.2, 0.2, 0.2, 0.4, 0.4, 0.4, 0.4, 0.4, 0.4, 0.4, 0.4,
0.4, 0.4, 0.4, 0.4, 0.4, 0.4, 0.4, 0.4, 0.4, 0.4, 0.4, 0.4, 0.4,
0.4, 0.4, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6,
0.6, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6, 0.6), .Dim = c(23, 4))

delta <- structure(c(NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA,
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NA, NA, NA, NA, NA, NA, NA, NA, NA, 0, NA, NA, NA, 0, NA), .Dim = c(85,4))

Input data (from reference: '… dataJAGS.txt')

Cmax <-

5

Mmu <-

0.919

ntreat <-

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6, 7, 9, 20, 9, 9, 10, 8, 7, 12, 6, 11, 8, 11, 7, 6, 10, 9, 4,

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4L))

```
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NA, NA, NA, NA, NA, NA, NA, NA, NA, NA), .Dim = c(85L, 4L, 4L
))
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LIBRARY OF TREATMENT IDs

Treatment ID (pretreat)	Treatment Label	Treatment ID (posttreat)	Treatment Label
1	Placebo	1	Placebo
2	Acitretin 0.4 mg/kg/day	2	Acitretin 0.4 mg/kg/day
3	Apremilast 30 mg	3	Apremilast 30 mg
4	Dimethyl fumarate up to 720 mg	4	Dimethyl fumarate up to 720 mg
5	Methotrexate 7.5 to 25 mg	5	Methotrexate 7.5 to 25 mg
6	Cyclosporine 2.5 to 5 mg	6	Cyclosporine 2.5 to 5 mg
7	Etanercept 25 mg + Acitretin 0.4 mg/kg	7	Etanercept 25 mg
8	Etanercept 25 mg	8	Etanercept 50 mg
9	Etanercept 50 mg	9	Adalimumab 40 mg
10	Adalimumab 40 mg	10	Infliximab 5 mg/kg
11	Infliximab 5 mg/kg	11	Ustekinumab 45 or 90 mg
12	Ustekinumab 45 or 90 mg	12	Ustekinumab 90 mg
13	Ustekinumab 90 mg	13	Tildrakizumab 100 mg
14	Tildrakizumab 100 mg	14	Tildrakizumab 200 mg
15	Tildrakizumab 200 mg	15	Secukinumab 150 mg
16	Secukinumab 150 mg	16	Secukinumab 300 mg
17	Secukinumab 300 mg	17	Guselkumab 100 mg
18	Guselkumab 100 mg	18	Brodalumab 210 mg
19	Brodalumab 210 mg	19	Risankizumab 150 mg
20	Risankizumab 75 mg	20	Ixekizumab 80 mg
21	Risankizumab 150 mg	21	Certolizumab pegol 200 mg
22	Ixekizumab 80 mg	22	Certolizumab pegol 400 mg
23	Certolizumab pegol 200 mg	23	Bimekizumab 320 mg
24	Certolizumab pegol 400 mg		
25	Bimekizumab 320 mg		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Bimekizumab for treating moderate to severe chronic plaque psoriasis ID2692

Clarification questions

Company response

5th March 2021

File name	Version	Contains confidential information	Date
ID2692_Bimekizumab for psoriasis_UCB Pharma_Response to ERG clarification questions_05.03.21_AiC REDAC	**1**	**Yes**	**05.03.2021**

Section A: Clarification on effectiveness data

A15. Please provide methods and results of the assessment of inconsistency in each of the NMA models.

UBC Response:

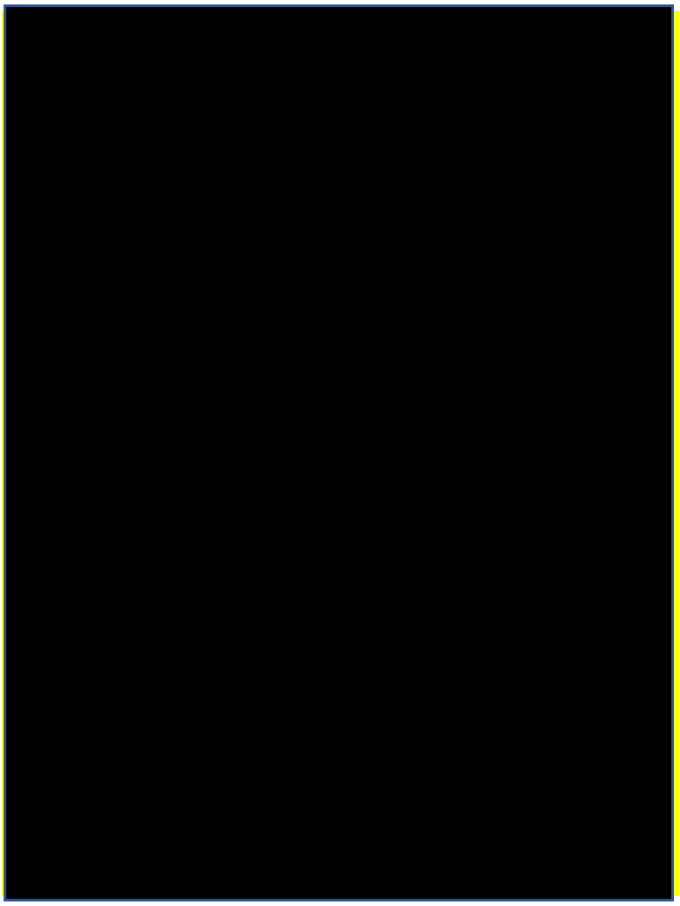
A more in-depth follow-up investigation of inconsistency was conducted, using an independent means model (or 'inconsistency model') as outlined in NICE DSU TSD4. Inconsistency was generally expected to be minimal, for several reasons, both empirical and statistical:

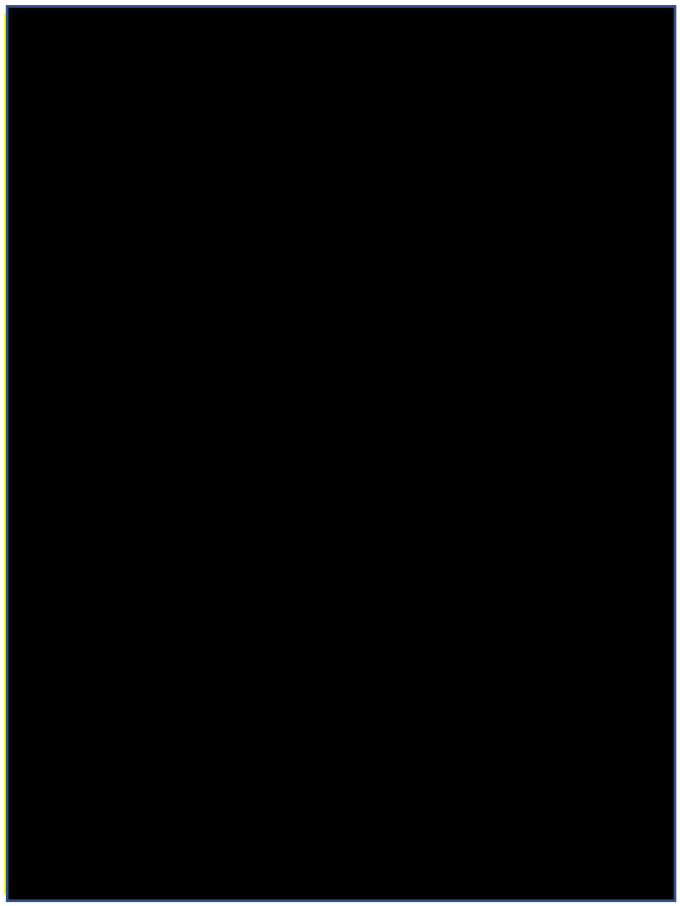
[redacted]

[redacted]

[redacted]

[redacted]





NICE National Institute for Health and Care Excellence

Patient organisation submission

Bimekizumab for treating moderate to severe chronic plaque psoriasis

Thank you for agreeing to give us your organisation's views on bimekizumab 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. [Please note that declarations of interests relevant to this topic are compulsory].

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	Chief Executive
4a. Brief description of the organisation (including who funds it). How many members does it have?	Patient Support Organisation and Charity. The reach of the Psoriasis Association now extends much further than that of the original member. The Psoriasis Association currently has around 2000 members who help to fund the organisation via an annual fee. Other sources of income include fundraising (individuals, legacies and trusts), Gift Aid, 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). The Psoriasis Association has three main aims; to provide information advice and support, to raise awareness and to fund and promote research. 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 (~14,000 registered users), and Social Media (~6,500 registered users on closed Facebook group). The main Psoriasis Association website averages 45,000 visits per month. Other social media channels used by the Psoriasis Association that lend themselves more to "raising awareness" include Twitter (~12,000 followers) and Instagram (~7,250 followers), along with a YouTube channel offering further information. The Psoriasis Association has been passionate about research throughout its 50+ year history. Regularly funding PhD studentships, alongside supporting the PPI of bigger research collaborations, always seeking to improve the lives of those affected by psoriatic disease.
4b. Has the organisation received any funding from the manufacturer(s) of bimekizumab and/or	Yes – UCB – £1,500 corporate membership, £2,500 emergency COVID-19 support, £2,193.91 matched fundraising Abbvie - £1,500 corporate membership, £6,500 core funding, £5,000 emergency COVID-19 support Almirral - £5,000 emergency COVID-19 support Amgen – £1,500 corporate membership, £8,500 emergency COVID-19 support Eli Lilly – £1,500 corporate membership, £5,000 emergency COVID-19 support

comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Janssen – £412.50 honorarium, £5,000 emergency COVID-19 support, £10,000 core funding LEO Pharma - £1,500 corporate membership, £5,000 emergency COVID-19 support
4c. 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 carers to include in your submission?	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:- the Psoriasis Association website (519,922 visitors in 2020) helpline (1892 enquiries in 2020) online forums (15,829 registered users in 2020) social media channels (including Facebook Group (this is a closed group with 6,881 registered users in 2020), Twitter (13,197 followers in 2020) and Instagram (10,344 followers in 2020) The Psoriasis Association analyses the data gathered from all communication channels (mentioned above) and monitors for trends in addition to interesting new requests. We have completed a Priority Setting Partnership on Psoriasis which gave valuable insight into issues affecting people living with

	psoriasis and psoriatic arthritis and are part way through supporting a Priority Setting Partnership on psoriatic arthritis specifically.
Living with moderate to severe plaque psoriasis	
6. What is it like to live with moderate to severe plaque psoriasis? What do carers experience when caring for someone with the condition?	Psoriasis is a lifelong condition with varying degrees of severity. It is a condition that causes great distress to patients and great frustration in what feels like a constant battle to access appropriate services and medications. The patients for whom this treatment (Bimekizumab) 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. It often impacts on sleep, work ability and social interactions. The scales are unsightly, and can cause problems with employment and work colleagues in many industries. Owing to the treatment ladder and trial and error approach of treating psoriasis, patients for whom this treatment is intended will have lived with this highly visible, painful and itchy condition for a number of years. They will have experienced the highs and lows of many treatment expectations and realities and invariably they will have experienced negative effects of living with psoriasis, impacting on their life and life potential. 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. Social isolation limits ability to form close relationships (as the opportunity to meet people decreases) and so dependence on family members can ensue. 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 with topical therapies. 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, carers, healthcare workers, even 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. Owing to the largely unpredictable nature of psoriasis, along with its' response to treatments, patients often experience highs and lows along their treatment journey. There is always great hope when a different treatment is able to be prescribed, their skin is deemed to be "bad enough" to now warrant a traditional systemic or biologic treatment. Often there is a period of elation when improvements to the skin are noticed. The impact of a quick response should not be under-estimated – it can often give people the confidence to get married or attend an interview for example, even visit a hairdresser / barber. Sadly, and all too often there then comes a low when the treatment stops working, or the side effects experienced means it must be discontinued. This cycle is then repeated over and over. Patients therefore need access to treatments that are appropriate, suitable and reliable over a long-term.

Current treatment of moderate to severe plaque psoriasis in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There is a very real postcode lottery in terms of care available on the NHS which sadly has worsened during the covid-19 pandemic. It is often difficult (and a long wait) for patients who need to re-access secondary care services when their psoriasis flares (often post-discharge from successful UV therapy). It is disconcerting, and unfair that patients are aware of further treatments that they are entitled to access only for there to be a delay, often in excess of a year before an appointment with the relevant healthcare professional can be made. 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. For many people with psoriasis 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. It is incredibly frustrating when NICE Guidelines and Technology Appraisals are over-ruled at a local level. There are many treatments that are theoretically available, but in practice are denied to patients e.g. due to local formularies, and restrictions as to how many opportunities a patient is entitled to try newer treatments. It is worth remembering that treatments are still trial and error in psoriasis, and so a large armourmentarium is necessary in order to manage this lifelong disease.
8. Is there an unmet need for patients with moderate to severe plaque psoriasis?	Yes – until we can better target therapies, or until we have a therapy that doesn't ultimately lose efficacy, there will remain an unmet need for patients with psoriasis. Pre-covid, the waiting times from point of referral to appointment in secondary care were around 8-10 months. Sadly this situation has become much worse. Therefore it is imperative that people with moderate-severe psoriasis are offered the most appropriate treatment at the first opportunity, and not left on suboptimal therapies. The reluctance to change therapies when unable to have face to face

	appointments is also resulting in patients remaining on suboptimal therapies for even longer – they must have better access to these drugs that have been licensed to treat their condition.
Advantages of bimekizumab	
9. What do patients or carers think are the advantages of bimekizumab?	The dosing regime of Bimekizumab is particularly advantageous to patients – an injection once every 8 weeks allows greater freedom to get on with one's life (from taking delivery and storage of more frequent injections to being able to travel without worry of transporting delicate treatments). Owing to the current climate (in relation to COVID-19) patients are also more conscious about vaccinations and when they fit within their treatment cycles. An 8 week dosing regime gives good flexibility when scheduling other healthcare requirements. The studies (trials BE SURE, BE READY AND BE RADIANT) show a good response under scrutiny (PASI 100 or PASI 90 and DLQI of 0 or 1). These high levels of response are particularly important to patients.
Disadvantages of bimekizumab	
10. What do patients or carers think are the disadvantages of bimekizumab?	Some patients remain concerned regarding the use of injections. Others may be a little apprehensive having to administer two injections per dose.

Patient population	
11. Are there any groups of patients who might benefit more or less from bimekizumab than others? If so, please describe them and explain why.	Those for whom other treatments have failed – many people with moderate to severe psoriasis will eventually lose efficacy from biologic treatments and, as psoriasis is a lifelong condition, it is essential to have new options for this cohort to move on to. People whose psoriasis may initially respond well and then they lose the response, the uniqueness of combining IL-17A and IL-17F can help with longevity of response, therefore decreasing the potential number of times a person may have to switch treatments.
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. The increased use of telephone or video consultations can also cause issues with assessing the severity of psoriasis (in all skin types). The psychological impact is being overlooked with many consultations regressing to speaking about the physical manifestations only. The true severity of psoriasis may therefore be being under-estimated and so patients under-treated / denied access to biologics. Early access to effective treatments is necessary in order to limit the negative life course impairment associated with this debilitating disease.

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Psoriasis is a lifelong condition in which individuals respond differently to different treatments. For this reason a range of treatment options for all degrees of severity is required.
- There is currently unmet need in the treatment of people with moderate psoriasis (for whom topical treatments nor biologics are suitable), and those where 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.
- Both quick response and long-term / long-acting / long-term efficacy are essential to the patient population.
- Access to effective treatments early in the course of the disease could greatly improve outcomes for patients who are not currently able to achieve their full life potential.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Bimekizumab for treating moderate to severe chronic plaque psoriasis

Thank you for agreeing to give us your organisation's views on bimekizumab 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. [Please note that declarations of interests relevant to this topic are compulsory].

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
3. Job title or position	Chief executive
4a. Brief description of the organisation (including who funds it). How many members does it have?	A patient-centred charity that exists to support people affected by psoriasis and psoriatic arthritis. Activities include information both in print and via a comprehensive website. Telephone support offering help, advice and a sign-posting service to other resources is also available. The organisation also supports research via a small grants scheme. Health care professionals continued professional development is promoted and supported with an accredited online training resource (free to NHS staff). There is no formal membership of the organisation, but subscriptions are available to receive a bi-annual journal, all other patient resource and support are free and can be accessed anonymously. Access to the website is also free, with limited sign-up details needed to enter the PAPAA Knowledge Bank and online subscriber's area. Use of social media is also part of the organisation's activities, but with a strict policy of only publishing evidenced-based and reliably sourced content. Funding is via donations, journal subscriptions, online shop sales, fundraising activities and an ethical investment portfolio. No funds are currently accepted from commercial organisations (including the pharmaceutical industry) or third party agents representing or supporting those sectors.
4b. Has the organisation received any funding from the manufacturer(s) of bimekizumab and/or comparator products in the last 12 months? [Relevant	No

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. 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 carers to include in your submission?	The information used in this submission has been gathered and based on direct feedback from people affected by psoriasis, and my personal experience of living with psoriasis. PAPAA also has a continuing data gathering process, and since 2014 via the PAPAA survey. All survey data we use is unpublished and for our own internal use. Those who identified as having moderate to severe psoriasis in our surveys used for this submmision N=411, age range 18-76. The surveys are predominately completed by females (246) male (102) non-disclosed (63), but psoriasis generally affects both men and woman equally.
Living with moderate to severe plaque psoriasis	
6. What is it like to live with moderate to severe plaque psoriasis? What do carers	For many people psoriasis can be very mild and not affect them or interfere with their daily lives, but when the condition moves beyond being mild to moderate, and becomes moderate to severe, the experience of living with psoriasis starts to change. The following are quotes from people who have moderate to severe psoriasis and reflect the overall views of what and how the condition affects their education, work, social life and relationships:

experience when caring for someone with the condition?	“It itches and burns all day. I can’t wear what I want because of how uncomfortable it makes me feel” “Extremely self-conscious at school. Would cover up” “It affected my focus when studying or in class as all I wanted to do was scratch my skin off. Also I was bullied by other kids due to it” “I missed lots of days at school to visit the hospital for treatment.” “The daily itching is painful and distracting. Scalp psoriasis and inside my ears. Ears were always infected. Made listening hard if they had been packed with gauze at hospital. Psoriasis on legs, teased by peers.” “I was bullied relentlessly at school and a lot of days off due to appointments and treatment.” “With the pain and constantly feeling uncomfortable because of the burning and itching sensations it affects my moods and is a huge distraction” “Can be difficult to dress appropriately and move comfortably.” “I constantly want to scratch myself. I also feel like it makes me look dirty to other people, like they think the flakes in my hair is dandruff when it's not sensitive area psoriasis.” “Psoriasis on hands and underneath my feet can make any type of work difficult.” “The flaking affects my appearance and I’m constantly itching and applying cream.” “Skin is greatly improved due to biological drug used to treat psoriatic arthritis.” “Work colleagues and patients continually commented on it which made me uncomfortable. Pain from the plaques cracking made working uncomfortable.”

	“Affected work when I had flares and when I had to attend hospital appt's every day for treatments for months on end.” “Simply trying to concentrate on an email can be tricky when I itch and burn so bad.” I had to give up caring, I do a less active role now. “I’ve lost all confidence in myself and hate the skin I’m in, making intimacy too painful.” “I refuse to be intimate with my partner or wear more revealing clothing.” “Twin beds now, as the plaques were in the bed and my scratching was irritating my partner.” “I feel unattractive when my skin flares. Do not wish to go out socialising either.” “My husband has to cream my body for me, sex is a thing of the past.” “I feel embarrassed to be seen naked; sore cracked skin under breasts and intimate areas.” “… as a younger person, boys would shy away from me due to my skin.” “I don’t want to go out and socialise if I can’t feel good or comfortable in what I’m wearing.” “I’ve had days where I’ve thought I don’t care what others think and will show my skin and strangers have come up to me and commented on how disgusting my skin is.” “I don't want to go out anywhere in case I have to wear something that might show my psoriasis.” “Red scalp as a child, scratching weeping scalp, equals bullying.” “Little interest in going out with scabby hands and feet. Wearing anything other than flip flops is difficult.”

	"I'm so conscious of what I wear due to flaking." I didn't have a social life for years. It limits what clothes I can wear as I always try to hide it "Wouldn't go swimming or wear shorts or short sleeves when I was younger." "Paranoid about flakes and scratching. Paranoid about skin when out in public." The key issues raised by those completing our surveys are not only the appearance of psoriasis, but also the impact of the pain, itch and soreness that psoriasis causes and the subsequent effect these have on daily function. Not least work and education but choice of clothing and the restrictions that causes. The psychological affect can be enormous and that affects how people feel and also causes problems with relationships, both those that are new and long-term. Psoriasis can become a lonely disease and leave people feeling inadequate, unloved and alienated.
Current treatment of moderate to severe plaque psoriasis in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There is an increased positivity towards newer therapies, but access is often frustrating to patients, with the feeling that they are not being offered the best therapies or are being offered less effective lower costing therapies. There is also a concern that given psoriasis is life-long that once therapies begin to fail that there won't be sufficient alternative treatments going forward.

8. Is there an unmet need for patients with moderate to severe plaque psoriasis?	The need to have options as therapies begin to fail or stop working is always a fear and will continue to be an unmet need. Choice, accessibility and options are a particular concern of patients with psoriasis.
Advantages of bimekizumab	
9. What do patients or carers think are the advantages of bimekizumab?	Adding an alternate to the existing treatment range and therapy that provides a different target if similar class therapies fail.
Disadvantages of bimekizumab	
10. What do patients or carers think are the disadvantages of bimekizumab?	As bimekizumab is not in general use for psoriasis, there doesn't appear to be any obvious disadvantages than other similar class therapies.

Patient population	
11. Are there any groups of patients who might benefit more or less from bimekizumab than others? If so, please describe them and explain why.	Those who have both psoriasis and psoriatic arthritis might benefit from a therapy that is beneficial in both conditions.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware.

Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Life-long condition with no cure
- Treatments often fail, therefore wide choice needed
- Psoriasis causes significant negative impact on quality of life
- Relationships, education and work impacted by psoriasis
- Psychological impact should not be underestimated

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Bimekizumab for treating moderate to severe chronic plaque psoriasis

Thank you for agreeing to give us your organisation's views on bimekizumab and its possible use in the NHS.

You can provide a unique perspective on bimekizumab 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.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted], **on behalf of the British Association of Dermatologists' Therapy & Guidelines sub-committee**
2. Name of organisation	**British Association of Dermatologists**

3. Job title or position	**Consultant Dermatologist**
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 moderate to severe plaque psoriasis? ☒ 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 not-for-profit organisation 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.
4b. Has the organisation received any funding from the manufacturer(s) of bimekizumab and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and	The BAD is a registered charity and owns various companies. The British Association of Dermatologists Biologic Interventions Register (BADBIR) is the national psoriasis biologic and systemic treatment registry (and an NIHR portfolio study) run by the BAD as a non-profit-making limited company. This company receives funding from most manufacturers of biological drugs for psoriasis on the registry to collect pharmacovigilance data. The BAD does not receive any funding from BADBIR.

purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
The aim of treatment for moderate to severe plaque psoriasis	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• Control of psoriasis with the aim of a 'clear' or 'nearly clear' by Physician's Global Assessment rating • Reducing the impact of the disease on quality of life
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Current guidelines (specifically the published 2020 BAD guidelines on biologic therapies for psoriasis), and prior NICE STAs have defined a minimum clinically significant improvement as: • ≥ 50% reduction in baseline disease severity, e.g. a PASI50 response, or percentage BSA where PASI is not applicable, and • Clinically relevant improvement in physical, psychological or social functioning (e.g. ≥ a 4-point improvement in DLQI score or resolution of low mood)
8. In your view, is there an	Yes – in real-world practice, not all people with psoriasis who fulfil NICE criteria for biologic therapy respond to

unmet need for patients and healthcare professionals in moderate to severe plaque psoriasis?	existing biologic therapies; secondary failure is also common (Patterns of biologic therapy use in the management of psoriasis: cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). Br J Dermatol. 2017 May;176(5):1297-1307. doi: 10.1111/bjd.15027. Epub 2017 Mar 20. PubMed PMID:27589476; Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015 Nov;135(11):2632-2640. doi: 10.1038/jid.2015.208. Epub 2015 Jun 8. PubMed PMID:26053050; Differential Drug Survival of Second-Line Biologic Therapies in Patients with Psoriasis, J Invest Dermatol. 2018 Apr;138(4):775-784. doi: 10.1016/j.jid.2017.09.044. Epub 2017 Dec 6.) **N.B.** Additional reference: Biologics may be less effective in the real world, cf. to trial data due to use of biologic therapies. Comparison of Drug Discontinuation, Effectiveness, and Safety Between Clinical Trial Eligible and Ineligible Patients in BADBIR JAMA Dermatol. 2018 May 1;154(5):581-588. doi: 10.1001/jamadermatol.2018.0183. Use of biologic therapy in the UK is currently limited to those with severe disease as defined by a PASI 10. This excludes use of highly effective biologic therapy (within the licensed indication – i.e. moderate or severe) where the disease is associated with a severe impact on their QoL, physical, social or psychological function. Specifically, people with moderate disease and those with severe disease but of limited extent – i.e. high-need areas such as the face, hands, feet, flexural/genital sites. People in these two groups will not have a PASI score of 10 but nevertheless will suffer major impact from their disease. Options for these patients are profoundly limited if methotrexate is not effective or cannot be tolerated. Newer small molecule drugs (e.g. dimethyl fumarate and apremilast) are not approved by NICE for patients with a PASI <10 either. Therefore, we would strongly suggest that the NICE CG153 criteria used for non-biologic systemic therapy be generalised to biologic therapy, i.e. psoriasis that cannot be controlled with topical therapy, and: • has a significant impact on physical, psychological or social wellbeing, and • one or more of the following: o psoriasis is extensive or o psoriasis is localised and associated with significant functional impairment and/or high levels of distress or o phototherapy has been ineffective, cannot be used or has resulted in rapid relapse. Including these indications with the NICE criteria would still be entirely consistent with the licensed indications for

	these treatments (moderate to severe psoriasis).
What is the expected place of bimekizumab in current practice?	
9. How is moderate to severe plaque psoriasis currently treated in the NHS?	With NICE-approved biologic therapies and biosimilars; apremilast; dimethyl fumarate; standard systemic therapies (see NICE CG153).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes – BAD guideline for biologic therapy for psoriasis 2020 https://onlinelibrary.wiley.com/doi/10.1111/bjd.19039 and NICE CG153 www.nice.org.uk/guidance/cg153. Please note the following comments regarding the final scope: ➔ There should be mention of psoriatic arthritis as an important, common co-morbidity and that when present, of the standard systemic therapies used in psoriasis, only methotrexate is helpful for both joints and skin. As previously communicated for more recent biologic STAs for psoriasis, the final scope mentions that "most treatments reduce the severity of psoriasis flares rather than prevent episodes" – there is no evidence that any of the treatments are disease-modifying. This would better describe the point being made here (rather than "most treatments reduce the severity….") as many of the new biologic treatments do clear or nearly clear the disease and maintain it in this state.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes – please see NICE CG153. Data from BADBIR national pharmacovigilance registry suggest that most people with psoriasis fulfil stipulated criteria, e.g. PASI mean (SD) = 16.4 (8.3) – please see Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. Br J Dermatol. 2015 Aug;173(2):510-8. doi: 10.1111/bjd.13908. Epub 2015 Jul 6. PubMed PMID:25989336. **N.B.** Clinical re-audit report based on CG153 standards www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-audits/psoriasis/psoriasis-2017 (July 2018) and

	https://onlinelibrary.wiley.com/doi/full/10.1111/ced.14286 (May 2020)
• What impact would bimekizumab have on the current pathway of care?	An additional option to consider in people with severe psoriasis; another agent with a novel mode of action, i.e. inhibition of both IL-17A and IL-17F cytokines More agents within the same 'market' may provide motivation to drive down the NHS price for other biological drugs in psoriasis, reducing overall NHS costs. A novel mode of action offers the opportunity to further study and clarify personalised treatment for psoriasis in the future.
10. Will bimekizumab be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – biologic therapy is a well-established intervention for psoriasis.
• How does healthcare resource use differ between bimekizumab and current care?	There would not be any expected differences in health resource use compared to existing NICE-approved agents aside from drug acquisition costs.
• In what clinical setting should bimekizumab be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist clinics.
• What investment is needed to introduce bimekizumab? (For example, for facilities, equipment, or training.)	No additional investment would be required.

11. Do you expect bimekizumab to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect bimekizumab to increase length of life more than current care?	N/A.
• Do you expect bimekizumab 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. In addition, bimekizumab has been trialled directly against three commonly used biologics, adalimumab (DATA ABSTARCT FORM EADV 2020), ustekinumab (DATA ABSTRACT FORM AAD 2020) and secukinumab (PRESS RELEASE DATA ONLY). In all three studies, bimekizumab was found to have superior efficacy to all three agents which are the three currently most commonly used in the UK. With this greater efficacy improved health-related quality of life is seen,
12. Are there any groups of people for whom bimekizumab would be more or less effective (or appropriate) than the general population?	Across the phase III program, bimekizumab was effective in all subgroup analyses with no clear group where it would appear to have differing effectiveness. As with all clinical trials, approximately 1/3 of patients who are treated in the real world are excluded so as with all therapies real-world data are needed.
The use of bimekizumab	
13. Will bimekizumab be easier	Biologic therapy has been available on the NHS for people with psoriasis who meet the eligibility criteria – and there

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.)	are no expected differences in use or practical implications with bimekizumab compared with other biologics.
14. Will any rules (informal or formal) be used to start or stop treatment with bimekizumab? Do these include any additional testing?	The published 2020 BAD guidelines recommended biologic therapy for the following people with psoriasis: Offer biologic therapy to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated [see National Institute for Health and Care Excellence (NICE) guidelines CG153] and the psoriasis has a large impact on physical, psychological or social functioning [for example, Dermatology Life Quality Index (DLQI) or Children's DLQI > 10 or clinically relevant depressive or anxiety symptoms] and one or more of the following disease severity criteria apply: • the psoriasis is extensive [defined as body surface area (BSA) > 10% or Psoriasis Area and Severity Index (PASI) ≥ 10] • the psoriasis is severe at localized sites and associated with significant functional impairment and/or high levels of distress (for example nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures and genitals).

	These criteria do extend to additional (small) subsets of people with psoriasis currently not covered by the NICE criteria for biologic therapy and were introduced due the limitations of the PASI disease severity tool (i.e. it is strongly dependent on body surface area affected, and for some people with localised disease at high-need sites the PASI will not reach 10) and the specific burden (and limited options) for people with disease in both compartments (skin and joint). Generally, therapy is stopped when: • the minimal response criteria are not met, either initially or further down the line (i.e. secondary failure) • adverse effects arise, e.g. development of neurological symptoms suggestive of demyelinating disease, or new/worsening pre-existing heart failure • the risks outweigh the benefits in a) pregnant females or females planning conception and b) people undergoing elective surgery • live vaccines need to be administered. No additional testing from what is already recommended for biologics.
15. Do you consider that the use of bimekizumab will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes – the calculation of the QALY does not encompass time off work, costs of emollients and other health care products bought by the patients, or other limitations that psoriasis imposes (e.g. social isolation, avoidance of relationships, stigma, depression, anxiety) or the (often significant) impact it has on family and carers. Further, comorbidities common in psoriasis (psoriatic arthritis, metabolic syndrome, cardiovascular disease) may not be appropriated to the psoriasis. The preferred QoL measure for psoriasis at present is the DLQI, and whilst it is important as it covers domains not specifically captured by EQ5D, it does not capture anxiety and depression (which are common in psoriasis). Thus, if the QALYs have been derived using DLQI then it may underestimate the impact; further, we know that the mapping algorithms are not necessarily accurate and so the accuracy of the QALY calculation will depend on the algorithm. A new tool based on real-world data is now available (Generating EQ-5D-3L Utility Scores from the Dermatology Life Quality Index: A Mapping Studying Patients with Psoriasis, Value in Health, article in press DOI: https://doi.org/10.1016/j.jval.2017.10.024). It would be interesting to know if the biosimilar drug acquisition costs will be used in the cost-effectiveness analyses.

16. Do you consider bimekizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Targeting both the IL-17A and IL-17F cytokines is a new treatment approach for psoriasis. Prior biologics which inhibit IL17 have only blocked the cytokine IL-17A (secukinumab, ixekizumab) and there is considerable evidence that IL17F also has an important role in the immunopathogenesis of psoriasis.
• Is bimekizumab a 'step-change' in the management of the condition?	Antagonism of both IL-17A and IL-17F pathways represent a step-change in the management of people with moderate-to-severe psoriasis. This is supported by bimekizumab's superior responses in clinical trials to: Adalimumab (an anti-TNF) Ustekinumab (IL12/23 blocker) Secukinumab (IL17A blocker; press release data only)
• Does the use of bimekizumab 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 bimekizumab affect the management of the condition and the patient's quality of life?	Bimekizumab appears to have a broadly comparable safety profile with other biologic therapies, although there is currently little data about its safety in a real-world population. It will be imperative that appropriate pharmacovigilance is put in place. In the clinical trials published to date, bimekizumab had a higher candida rate that other IL-17 blockers, although this side effect was in the main easily managed.
Sources of evidence	
18. Do the clinical trials on bimekizumab reflect current UK clinical practice?	Yes, especially given the three head-to-head comparator studies compared the efficacy and safety of bimekizumab against the three most commonly prescribed drugs for psoriasis over the last 3 years in the UK.
• If not, how could the results be extrapolated to the UK setting?	N/A.
• What, in your view, are the most important outcomes, and were they measured in the trials?	**The following outcomes were reported in the trials:** PASI100, PASI90, PASI75, IGA clear/almost clear, serious AEs, suicide ideation and behaviours, depression and anxiety (HADS). All these outcomes are important and relevant. Other outcomes that may not have been reported but are highly relevant include: • **Psoriasis improvement on the face, scalp, nails:** Plus, other high-need sites, i.e. hands and feet, flexural/genital psoriasis. • **Response rate:** Over what time period? It would be important to include longer treatment outcomes. • **Relapse rate:** over what time period? It would be important to include longer treatment outcomes.

	• **Adverse effects of treatment:** infection; separate out adverse effects in the very short term, e.g. during loading doses. • **Health-related quality of life (including dermatology quality of life index [DLQI]):** Include other measures of impact, e.g. on psoriatic arthritis. • **Impact on concomitant psoriatic arthritis**.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	See notes above.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There is very limited information about use of the technology outside clinical trials. It would be extremely important for all people with psoriasis who meet the eligibility criteria to be enrolled in BADBIR when prescribed this agent to ensure capture of high-quality pharmacovigilance data and to allow relevant comparisons with other biologic agents (N.B. around 20,000 patients now registered – please see www.badbir.org). We suggest featuring a future research recommendation in the final guidance, along the lines of that featured in the ustekinumab STA (TA180): "The collection of data on the use of ustekinumab and other biological therapies as part of the British Association of Dermatologists' Biologics Intervention Register (BADBIR)."
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No; however, it is worth pointing to the living systematic review and network meta-analyses by the Cochrane Skin Group: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance in this area?	No; however, ciclosporin cannot be used for > 1 year and is therefore a less relevant comparator for this STA. Similarly, PUVA is associated with increased risk of skin cancer and can only be used in the shorter term. The most relevant comparators are adalimumab and methotrexate.
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. Are infliximab and etanercept relevant comparators for bimekizumab in adults with moderate to severe plaque psoriasis?	These drugs are likely to be less effective than bimekizumab, are the two most rarely used biologic drugs for treating psoriasis and may not seem appropriate to include as comparators. It should be noted that the three most commonly prescribed biologics in the UK in recent years are adalimumab, ustekinumab and secukinumab.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Important addition, with a novel mode of action
- High efficacy rates, especially in relation to disease clearance
- Existing therapies, while effective for many, do not work for *all* those requiring treatment
- NICE criteria for biologic therapy – if applied here – limit access for people who would benefit (not just applicable to this technology)
- Head-to-head trials with the three most commonly used biologic drugs for psoriasis in the UK are imminently due for publication

Thank you for your time.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Bimekizumab for treating moderate to severe plaque psoriasis [ID2692]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 8 April 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, all information submitted as '[redacted] in yellow, and all information submitted as '[redacted] in pink.

Issue 1 Description of (co-) primary endpoints in the bimekizumab Phase 3 clinical trials

Description of problem	Description of proposed amendment	Justification for amendment
The following content is incorrect (ERG Report, p. 10): *"Co-primary endpoints were measured at week 16 and included:* • *a PASI 90 response in BE-READY, BE-VIVID, BE- SURE,* • *a PASI 100 response in BE-RADIANT and* • *for all four trials, an investigator's global assessment response (IGA) 0/1 response (represented by an IGA score of 'clear' (0) or 'almost clear' (1)) with at least a two-category improvement from baseline. "* BE RADIANT did not have co-primary endpoints, rather PASI 100 was the only primary endpoint and IGA 0/1 was included as a secondary endpoint.	This content should be corrected to: *"In BE-READY, BE-VIVID and BE-SURE, co-primary endpoints were measured at Week 16 and included:* • *a PASI 90 response;* • *an investigator's global assessment response (IGA) 0/1 response (represented by an IGA score of 'clear' (0) or 'almost clear' (1)) with at least a two-category improvement from baseline.* *In BE-RADIANT, the primary endpoint was PASI 100 at Week 16."*	This amendment is required to ensure that the design of BE RADIANT is accurately reported in the ERG report. This amendment will have no impact on the report, or its conclusions.

Issue 2 Description of the bimekizumab Phase 3 trials

Description of problem	Description of proposed amendment	Justification for amendment
Throughout the ERG report, the Phase 3 bimekizumab trials are referred to as BE-READY, BE-VIVID, BE-SURE and BE-RADIANT. The formal names for these trials do not include the hyphenation, and are therefore BE READY, BE VIVID, BE	UCB request that the ERG update the names of the bimekizumab Phase 3 clinical trials to not be hyphenated, throughout their report.	UCB request this amendment for accuracy of reporting of trial identifiers. This will not impact upon the report, or its conclusions.

SURE and BE RADIANT.		
In the description of the BE READY trial treatment regimens (ERG Report, p.11), it is not clear which treatments are subsequently received by Week 16 responders initially randomised to placebo. Furthermore, when stating that patients without a response at Week 16 or who relapsed during the withdrawal phase subsequently entered the open label bimekizumab 320 mg Q4W 'escape' arm, the timepoint for relapse during the withdrawal phase after which patients could enter the escape arm is not clear.	UCB request that the description of the BE READY treatment regimens be updated to clarify that Week 16 responders initially randomised to placebo remain on placebo after the initial treatment period. UCB also request that the ERG specify that patients were eligible to enter the bimekizumab 320 mg Q4W 'escape' arm following relapse, defined as no longer achieving a PASI 75 response at Week 20 or later.	UCB request that these amendments are made to ensure that the BE READY trial is described with sufficient clarity. This will not materially impact upon the report, or its conclusions.

Issue 3 Reporting of bimekizumab Phase 3 trial results

Description of problem	**Description of proposed amendment**	**Justification for amendment**
The following statement incorrectly lists the trials from which the reported results were pooled, and does not provide sufficient detail on the patient population to which the results correspond (ERG Report, p.12): *"A pooled analysis of BE-VIVID, BE-SURE and BE-RADIANT showed that a* [redacted] *with PASI 90, PASI 100 and IGA 0/1 responses at week 16 maintained the response* [redacted] *(CS Table 19)."* These results are derived from an analysis	It is proposed that this statement be amended to: *"A pooled analysis of BE-VIVID, BE-SURE and BE-READY showed that a* [redacted] *with PASI 90, PASI 100 and IGA 0/1 responses at Week 16 maintained the response at Week 52 (CS Table 19)."*	UCB request that this amendment is made to ensure that the Phase 3 bimekizumab trial results are accurately and clearly reported. This will not

of Pool E2, which pooled data from BE VIVID, BE SURE and BE READY (not BE RADIANT), and refer to patients treated with either bimekizumab 320 mg Q4W/Q8W or bimekizumab 320 mg Q4W.		materially impact upon the report, or its conclusions.
The following statement does not provide sufficient information regarding the timepoint at which relapse rate was measured (ERG Report, p.13): *"In BE-READY, the relapse rate (defined as not achieving a PASI 75 response at Week 20 or later) of patients who had a PASI 90 response at week 16 and who entered the randomised withdrawal phase was 11.3% for the bimekizumab Q4W arm and 9.0% for the bimekizumab Q8W arm compared to 73.3% for the placebo arm (CS section B.3.6.3)."*	It is proposed that this statement be amended to: *"In BE-READY, at Week 56, the relapse rate (defined as not achieving a PASI 75 response at Week 20 or later) of patients who had a PASI 90 response at Week 16 and who entered the randomised withdrawal phase was 11.3% for the bimekizumab Q4W arm and 9.0% for the bimekizumab Q8W arm compared to 73.3% for the placebo arm (CS section B.3.6.3)."*	UCB request that this amendment is made to ensure that the Phase 3 bimekizumab trial results are accurately and clearly reported. This will not materially impact upon the report, or its conclusions.

Issue 4 Reporting of Week 16 discontinuation rates in the placebo arms of the Phase 3 bimekizumab trials

Description of problem	Description of proposed amendment	Justification for amendment
The following statement is incorrect (ERG Report, p.14): *"Discontinuation rates were generally low at week 16 (around 3-6% of randomised patients, CS Appendix D.2) except in the placebo arms in BE-SURE and BE-VIVID*	It is proposed that this statement is corrected to: *"Discontinuation rates were generally low at Week 16 (around 3-6% of randomised patients, CS Appendix D.2) except in the placebo arm of BE-VIVID (11.8%)."*	This amendment is required to ensure that the placebo arm discontinuation rates reported in the ERG report accurately reflect the results of the bimekizumab clinical trials. This amendment will have no impact on the report, or its conclusions.

(10-12%)." The BE SURE trial does not have a placebo arm; furthermore, discontinuation rates of 10–12% were not observed in the only other trial with a placebo arm (BE READY; BE READY placebo arm discontinuation rate: 4.65% [4/86]).		

Issue 5 Reporting of how safety data were pooled across the bimekizumab clinical trial programme

Description of problem	Description of proposed amendment	Justification for amendment
The following statement does not fully describe which data were pooled for Pool S1 (ERG Report, p. 15): *"Pool S1 included data from the initial treatment period (weeks 0-16) of the placebo-controlled trials, BE-READY and BE-VIVID."*	UCB request that the ERG clarify that Pool S1 only considered data for bimekizumab and placebo; as such, patients who were randomised to ustekinumab in BE VIVID were not included in this safety analysis.	UCB request that this amendment is made to ensure that the pooling of safety data is clearly described. This amendment will have no impact on the report, or its conclusions.
The following statement does not fully describe which data were pooled for Pool S2 (ERG Report, p. 15): *"Pool S2 included data from the initial treatment, maintenance and open-label extension periods for all bimekizumab doses all Phase II and Phase III bimekizumab trials, except BE-RADIANT as this study was still blinded at the time of pooling."*	UCB request that the ERG clarify that Pool S2 considers patients treated adalimumab and ustekinumab in BE SURE and BE VIVID, as well as patients treated with all bimekizumab doses across all Phase 2 and Phase 3 bimekizumab trials. It will also be important to clarify that the ustekinumab and adalimumab data were not pooled with the bimekizumab trial data, rather Pool S2 allowed comparison of the pooled bimekizumab trial data with that of patients treated with adalimumab and ustekinumab. Alternatively, UCB request that this wording is adjusted to make it clear that it is only the bimekizumab data from Pool S2 that is being described here (not Pool S2 as a whole, which also includes data for ustekinumab and adalimumab).	UCB request that this amendment is made to ensure that the pooling of safety data is clearly described. This amendment will have no impact on the report, or its conclusions.

Issue 6 Reporting of safety data

Description of problem	Description of proposed amendment	Justification for amendment
The following statement is not fully correct (ERG report, p. 16): *"Pre-specified AESI were reported* [redacted] *(CS section 3.10.2)."* Some pre-specified AESI [redacted] not included in this list were reported in [redacted] of patients; furthermore, the values reported for [redacted] are incorrect.	This statement should be corrected to: *"Pre-specified AESI were reported* [redacted] *(CS section 3.10.2)."*	UCB request that this amendment is made to ensure that the safety data are accurately reported. This amendment will have no impact on the report, or its conclu

		sions.
The following statement is incorrect (ERG Report, p.24): *"and for SAEs [redacted]%) which were [redacted] with those observed for the cost comparator trials".* Based on the integrated summary of safety (Pool S1), the placebo response rate at Week 16 was [redacted].	This statement should be corrected to: *"and for SAEs [redacted]%) which were [redacted] with those observed for the cost comparator trials".*	UCB request that this amendment is made to ensure that the safety data are accurately reported. This amendment will have no impact on the report, or its conclusions.

Issue 7 Reporting of studies included in the company's network meta-analysis

Description of problem	Description of proposed amendment	Justification for amendment
The following statement does not	UCB request that this statement is updated to specify that this	UCB request that this amendment is made to

accurately reflect the studies included in the NMA: *"The indirect treatment comparison (NMA) presented in the CS comprises a total of 84 RCTs"* This statement is also made on p.13 of the ERG Report. The PASI NMA included 84 RCTs; for the NMAs of serious AEs and discontinuation due to AEs, the evidence network was as per the PASI analysis with the exception of an additional two studies identified in the SLR being added to the network for the discontinuation due to AEs outcome (Ellis, 1991 [cyclosporine and placebo] and M10-315 [etanercept and placebo]).	refers to the NMAs for PASI and serious AEs, but an additional two studies were included in the network for discontinuation due to AEs. UCB request that the clarifications are also made to the corresponding statements on p.13 of the ERG report.	ensure that the NMAs are accurately reported in the ERG report. This amendment will have no impact on the report, or its conclusions.

Issue 8 Description of the NMAs for safety outcomes

Description of problem	Description of proposed amendment	Justification for amendment
The following content does not specify the timepoint at which these outcomes were assessed in the NMA for safety outcomes (ERG Report, p.17): *"Safety* • *Serious adverse events (AEs)* • *Discontinuation due to adverse events (AEs)"*	UCB request that this content be amended to: *"Safety* • *Serious adverse events (AEs) at 10-16 weeks* • *Discontinuation due to adverse events (AEs) at 10-16 weeks"*	UCB request that this amendment is made to ensure that the safety NMA is accurately described in the ERG report. This amendment will have no impact on the report, or its conclusions.

Issue 9 Reporting of PASI NMA results

Description of problem	Description of proposed amendment	Justification for amendment
The following statement is not an accurate reflection of the content presented in the company submission (ERG Report, p. 18): *"The NMA results, however, are presented in accordance with the decision problem (i.e. only comparisons between biologics). The reason for including non-decision problem treatments in the network is not explicitly reported in the CS. The ERG therefore assumes their role is to provide additional evidence to the network to strengthen the relevant comparisons between bimekizumab and the other biologics."* Whilst UCB agree that it is true no comparisons between bimekizumab and non-biologic comparators are explicitly described in the submission, the forest plots of NMA results that are presented do include the results for the non-biologic systemic therapies that were included in the NMA (e.g. cyclosporine, methotrexate).	UCB request that the ERG revise this content to more accurately reflect the information provided within the company submission.	UCB request that this amendment is made to ensure that the write-up of the NMA results within the company submission is accurately described in the ERG report. This amendment will have no impact on the report, or its conclusions.

Issue 10 Reporting of treatment discontinuation rates explored in sensitivity analyses

Description of problem	Description of proposed amendment	Justification for amendment
The following statement is not correct (ERG Report, p.28): *"The company vary this rate in sensitivity analysis by -/+ 20% (16% to 20% annual*	UCB request that the statement is corrected to: *"The company vary this rate in sensitivity analysis by -/+ 20% (16% to 24% annual discontinuation)."*	This amendment has been requested to ensure that the modelling approach is accurately reported in the ERG report. This clarification will have no impact on the report,

discontinuation).” The discontinuation rate was varied between 16% and 24% in the sensitivity analyses.		or its conclusions.

Issue 11 List price for risankizumab

Description of problem	Description of proposed amendment	Justification for amendment
The list price for risankizumab is incorrectly reported in Table 2 (Dosing and list prices for bimekizumab and comparators; ERG Report, p.28).	UCB propose that the risankizumab list price is updated to be £3,326.09, which is the value reported in the company submission and used in the economic analysis.	This amendment has been requested to ensure that the modelling approach is accurately reported in the ERG report. This clarification will have no impact on the report, or its conclusions.

Issue 12 Regulatory update

Description of problem	Description of proposed amendment	Justification for amendment
The ERG Report (p.29) states that: *“CS Table 2 notes that:* [redacted] .” UCB would like to provide the ERG with an update on the draft posology wording following recent receipt of the [redacted] from the ongoing regulatory assessment; it is now anticipated that the label will include the following wording related to the [redacted]	UCB request that the ERG consider their report and economic analyses in light of this regulatory update. UCB would also like to take this opportunity to reiterate that [redacted]	UCB update provided to the ERG and

[redacted] Please note that this wording continues to be draft and subject to final regulatory approval.		NICE for information.

Issue 13 Table 4 caption

Description of problem	Description of proposed amendment	Justification for amendment
The caption for Table 4 is incorrect (ERG Report, p.32): *"Table 4 Company's sensitivity and scenario analyses – list price for bimekizumab and comparators"* Table 4 includes sensitivity and scenario analyses conducted by the ERG, some of which were not conducted by UCB as part of the company submission.	UCB request that the caption for Table 4 is updated to be: *"Table 4 ERG's sensitivity and scenario analyses – list price for bimekizumab and comparators"*	This amendment has been requested to ensure that it is clear these analyses were conducted by the ERG. This clarification will have no impact on the report, or its conclusions.

Issue 14 Typographic errors

Description of problem	Description of proposed amendment	Justification for amendment
The following statement contains a spelling error (ERG Report, p.20): *"However, as stated above, the company's preference was to adjust for baseline risk and to maintain consistency with previous cost comparison appraisals (TA521 guselkimab; TA596 risankizumab).*	UCB advise that the spelling of guselkumab is updated.	Typographic error. This amendment will have no impact on the report,

		or its conclusions.
The following statement contains a spelling error (ERG Report, p.23): [redacted] "	UCB advise that the spelling of PASI is updated.	Typographic error. This amendment will have no impact on the report, or its conclusions.
The following statement contains a spelling error (ERG Report, p.24): *"The trials have compared bimekizumab with placebo and three biologic treatments: adaliumumab, ustekinumab and secukinumab."*	UCB advise that the spelling of adalimumab is updated.	Typographic error. This amendment will have no impact on the report, or its conclusions.
The following statement contains a typographic error (ERG Report, p. 31): *"Uncertainty over model assumptions was assessed with one-way sensitivity analyses (presented in CS Figures 21-23) and scenario analyses (CS Figure 31)."* The scenario analyses are presented in Table 31 of the company submission.	UCB advise that the statement is updated to be: *"Uncertainty over model assumptions was assessed with one-way sensitivity analyses (presented*	Typographic error. This amendment will have no impact on the report, or its conclusions.

	in CS Figures 21-23) and scenario analyses (CS Table 31)."	

Updates to confidentiality highlighting

Location of incorrect marking	Description of incorrect marking	Amended marking
ERG Report, p.6	To protect the confidentiality of the NMA results, the following statement should be marked as academic in confidence: "[redacted]".	[redacted]
ERG Report, p. 12	The timeframe for maintenance of response in the following statement does not need to be marked as academic in confidence: *"A pooled analysis of BE-VIVID, BE-SURE and BE-RADIANT showed that a* [redacted] *with PASI 90, PASI 100 and IGA 0/1 responses at week 16 maintained the response* [redacted] *(CS Table 19)."* Please note that this statement also incorrectly references BE RADIANT instead of BE READY (see Issue 3 above); the amended marking has therefore been provided on the corrected text.	*A pooled analysis of BE-VIVID, BE-SURE and BE-READY showed that a* [redacted] *with PASI 90, PASI 100 and IGA 0/1 responses at week 16 maintained the response at week 52 (CS Table 19)*
ERG Report, p. 14	In the following statement, the proportion of UK patients in the bimekizumab Phase 3 trial populations should be marked as academic rather than commercial in confidence: *"The ERG notes that UK patients represented less than* [redacted] *of the four trial populations".*	*The ERG notes that UK patients represented less than* [redacted] *of the four trial populations*

ERG Report, p.15	To protect the confidentiality of the BE RADIANT trial data, the data presented in this statement should be marked as academic in confidence: *"The proportion of patients who had previously used any systemic therapy ranged from [redacted] and the proportion who had previously used any biologic therapy ranged from [redacted]."* If unredacted, inferences could be made about the corresponding values for BE RADIANT.	*The proportion of patients who had previously used any systemic therapy ranged from [redacted] and the proportion who had previously used any biologic therapy ranged from [redacted]*
ERG Report, p.17	The formatting of the following statement needs updating to ensure that the appropriate content is marked as academic in confidence: *"Treatment-related TEAEs were [redacted] in bimekizumab trial arms (ranging from [redacted])".*	*Treatment-related TEAEs were [redacted] in bimekizumab trial arms (ranging from [redacted])*
ERG Report, p.21	To protect the confidentiality of the BE RADIANT trial data, the data presented in this statement should be marked as academic in confidence: *"The ERG notes that the proportion of patients in the bimekizumab phase III RCTs who had previously used biologics was in the range [redacted] thus at the upper end of the range for the network as a whole."* If unredacted, inferences could be made about the corresponding values for BE RADIANT.	*The ERG notes that the proportion of patients in the bimekizumab phase III RCTs who had previously used biologics was in the range [redacted] thus at the upper end of the range for the network as a whole*
ERG Report, p.23	To protect the confidentiality of the NMA results, the following statement should be marked as academic in confidence: *"In the NMA of safety outcomes [redacted] (CS, Figures 18, 19)."*	*In the NMA of safety outcomes [redacted] (CS, Figures 18, 19)*
ERG Report, p.24	The data marked as academic in confidence in the below content is not confidential and hence the confidentiality marking can be removed: *"The placebo response rate for PASI 75 ranged from [redacted]% in the bimekizumab trials (BE-READY and BE-VIVID) and [redacted] to*	*The placebo response rate for PASI 75 ranged from 2.3-7.2% in the bimekizumab trials (BE-READY and BE-VIVID) and was similar to that observed in key pivotal trials used to support NICE submissions for the cost comparator drugs*

	that observed in key pivotal trials used to support NICE submissions for the cost comparator drugs (risankizumab: 8.2 to 9.8%; brodalumab: 2.7-8.1%; ixekizumab: 2.4-7.3%). [6-8] Smaller placebo response rates were observed in the bimekizumab trials for PASI 90 ([redacted]) and PASI 100 ([redacted])"	*(risankizumab: 8.2 to 9.8%; brodalumab: 2.7-8.1%; ixekizumab: 2.4-7.3%).[6-8] Smaller placebo response rates were observed in the bimekizumab trials for PASI 90 (1.2-4.8%) and PASI 100 (0.0-1.2%)*
ERG Report, p.27	To protect the confidentiality of the NMA results, the AIC highlighting of this statement should be updated to cover the numerical results: [redacted]"	[redacted]

CONFIDENTIAL REPORT

Bimekizumab for treating moderate to severe chronic plaque psoriasis

ERRATUM following factual accuracy check by the company

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Declared competing interests of the authors

None

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Rider on responsibility for report

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

This report should be referenced as follows:

Hazell, L.; Lord, J.; Kalita, N.; Scott, D., and Shepherd, J. Bimekizumab for treating moderate to severe chronic plaque psoriasis. A NICE Technology Appraisal. Southampton Health Technology Assessments Centre, 2021.

Contributions of authors

Lorna Hazell critically appraised the bimekizumab clinical effectiveness evidence and drafted the report. Joanne Lord critically appraised the cost comparison analysis, and drafted the report. Neelam Kalita critically appraised the cost comparison analysis, and drafted the report. David Scott critically appraised the network meta-analysis and drafted the report. Jonathan Shepherd critically appraised the bimekizumab clinical effectiveness evidence, the network meta-analysis and drafted the report. He is the project co-ordinator and guarantor.

Please note that: *Sections highlighted in* [redacted] *are* [redacted]. *Sections highlighted in* [redacted]. *Figures that are AIC have been bordered with yellow.*

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

1.1 The technology is pharmacologically similar to the comparator

Bimekizumab is a humanised immunoglobulin monoclonal antibody that binds to both IL-17A and IL-17F cytokines to inhibit the IL-17 pathway. The company submission (CS) states that, if recommended, bimekizumab would be the only available plaque psoriasis treatment with this dual selective inhibition of IL-17A and IL-17F.

Two of the chosen cost comparators also target the IL-17 pathway: ixekizumab (IL-17A inhibitor) and brodalumab (IL-17A receptor inhibitor). Expert clinical opinion to the ERG is that bimekizumab might offer an advantage over standard IL-17 inhibitors due to the additional IL-17F inhibition. The third cost comparator is an IL-23 inhibitor (risankizumab).

The ERG's interpretation (confirmed by our clinical expert) is that, as a biologic drug, bimekizumab is similar, overall, to the chosen cost comparators. Pharmacologically it may have more similarity to the IL-17 agents than to the newer IL-23 agents. Amongst the IL-17 agents bimekizumab appears to be distinctive due to its dual selective inhibition of IL-17A and IL-17F. The company suggests that this potentially translates into greater clinical efficacy for bimekizumab compared to other biologics. The ERG's clinical expert agrees this is plausible, though it cannot be known for certain at present.

1.2 The selected comparator is appropriate

The ERG considers that the company's chosen cost-comparators (risankizumab, ixekizumab and brodalumab) adequately represent the NICE recommended treatments for plaque psoriasis as a whole. In the company's network meta-analyses these were the three highest ranking treatments on the PASI 75 efficacy measure (75% reduction in Psoriasis Area Severity Index) after bimekizumab. [redacted].

Risankizumab was recommended by NICE on the basis of cost-comparison to the biologic drug Guselkumab (TA596). Guselkumab itself was also recommended by NICE based on a cost-comparison to the biologic drugs ixekizumab and secukinumab (TA521). Ixekizumab (TA442) and brodalumab (TA511) were recommended by NICE based on cost-utility analyses in

comparison to multiple biologic drugs available at the time of those appraisals. Thus, the chosen comparators can be regarded to be representative of existing NICE recommended treatments.

Expert clinical advice to the ERG suggests that these three comparator drugs would be expected to have a reasonable market share in the treatment of plaque psoriasis.

The company states that the assumptions and methods informing the current cost comparison analysis maintain precedent with the two previous cost comparison NICE FTAs in this indication (TA596 Risankizumab, TA521 Guselkumab). Throughout this report we therefore note instances of concordance/discordance with previous NICE appraisals in this indication, specifically appraisals of the three cost-comparators (i.e. TA596, TA442 and TA511), and the remaining cost comparison FTA (i.e. Guselkumab TA521).

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

2.1 Population

The NICE scope specifies the relevant population as adults with moderate to severe plaque psoriasis. The marketing authorisation for bimekizumab is expected to be for [redacted]

The company's decision problem is more specific: adult patients with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated.

The decision problem is thus narrower than the scope and the marketing authorisation in terms of patient population. The company justifies this by stating their expectation that bimekizumab would be used as an alternative to other biologic therapies, specifically in adults with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. Furthermore, they state that the population aligns with the majority of previous appraisals for biologics in plaque psoriasis, including the most recently NICE recommended biologic, risankizumab (NICE TA596). The ERG considers this an acceptable justification for the purposes of this cost-comparison.

For patients on biologic treatment, the NICE psoriasis pathway states that switching to an alternative biologic should be considered if there is no response to a first biologic (primary failure), or response to a first biologic is subsequently lost (secondary failure), or intolerance or contraindication. Expert clinical advice to the ERG suggests that some patients may switch biologic treatments multiple times during the course of their disease. However, there is no recommendation regarding which biologic should be used first. Therefore, the ERG assumes that patients eligible for bimekizumab, therefore, may be either biologic naive or biologic experienced. This is of significance for judging the generalisability of the bimekizumab clinical trials (see section 3.2.3 of this report), and the assessment of heterogeneity in the indirect treatment comparison (section **Error! Reference source not found.**).

2.1.1 Psoriasis severity

The ERG notes that whilst the company's decision problem specifies inclusion of patients with moderate to severe plaque psoriasis, NICE guidance on previously appraised biologics stipulates they should be used in patients with severe disease (i.e. not in patients with moderate disease). The ERG asked the company to clarify this discrepancy (clarification question A2). In their response the company point out that previous scopes of NICE appraisals of biologics have included moderate to severe plaque psoriasis patients, despite final appraisal determinations (FADs) specifying their use in severe or very severe disease. To align with these previous appraisals the company's decision problem population includes moderate to severe psoriasis, but with the caveat that they expect a NICE recommendation for bimekizumab would similarly restrict its use to patients with severe disease (thus following NICE precedent).

The company's definition of severe psoriasis is identical to the definition of severe disease used in existing NICE guidance (i.e. based on PASI and DLQI score, and prior use of, or contraindication to, other systemic treatments and phototherapy). The ERG's clinical expert agrees that this indicates severe psoriasis.

The restriction of the decision problem to a narrower patient population has implications for the choice of comparator treatments in the scope, as discussed next.

2.2 Comparator

The NICE scope lists two sets of criteria with regard to relevant comparator treatments:

- Those for whom systemic non-biological treatment or phototherapy is suitable

- Those for whom conventional systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated

Given the restricted decision problem population, only the treatments available for 'adult patients with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated' are eligible comparators for bimekizumab. The company has selected three NICE recommended biologics for cost comparison to bimekizumab:

- Risankizumab (NICE TA596)
- Ixekizumab (NICE TA442)
- Brodalumab (NICE TA511)

In an FTA, eligible comparators have to have been recommended by NICE for the same indication as the current appraisal. Only one of the scoped comparators needs to be selected. In this instance all three of the company's chosen comparators meet this requirement.

2.3 Outcome

The outcomes specified in the company's decision problem are broadly aligned with those in the final NICE scope. The company did not have sufficient data to explore the impact of treatment on psoriasis of the face or genitals (included in the scope). This limitation was also noted in the NICE appraisals of the three cost comparators (TA596, TA442 and TA511).

The ERG notes that a PASI 90 or PASI 100 response (90% or 100% reduction in PASI score from baseline) is considered an important therapeutic goal, aiming to achieve complete or near complete clearance of psoriasis. However, the less stringent PASI 75 response (at least a 75% reduction in PASI score) has been considered an adequate measure to ensure continuation of therapy in previous NICE appraisals, and for this reason the company have selected it as the key input for the cost comparison in the current CS. The ERG's clinical expert considers PASI 75 to be a clinically meaningful indicator of response to induction therapy used in practice, and patients achieving this would then be considered eligible for maintenance therapy. Clinicians would aim for PASI90 or PASI100 response for patients on long-term treatment.

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

3.1 Clinical evidence submitted by the company

3.1.1 The company submission

The CS comprises a main evidence submission (Document B), a summary (Document A) and appendices to Document B. The company also provided relevant clinical study reports for bimekizumab and additional information in response to clarification questions from the ERG. Four multi-centre phase III/IIIb double-blind randomised controlled trials, BE READY, BE VIVID, BE- SURE and BE RADIANT, inform the clinical effectiveness evidence submitted by the company. These RCTS provide direct evidence of clinical effectiveness for bimekizumab compared to placebo and three different active comparators (ustekinumab, adalimumab and secukinumab). No head-to head trials are available comparing bimekizumab with the company's chosen cost comparators: risankizumab, brodalumab and ixekizumab. Results of a network meta-analysis (NMA) are therefore included in the CS to provide indirect evidence of clinical similarity between bimekizumab and the company's chosen cost comparators.

3.1.2 Trial design

Trial methodology for BE READY, BE VIVID, BE- SURE and BE RADIANT is summarised in CS section B.3.3.1 and participant flow is described in CS Appendix D.2. All four trials included patients ≥ 18 years old with plaque psoriasis for at least six months prior to screening who were candidates for systemic therapy and/or phototherapy. Patients were required to have moderate to severe plaque psoriasis defined by a PASI score ≥12, affected body surface area (BSA) ≥10% and IGA score ≥3 on a 5-point scale.

All four trials consisted of an initial 16-week treatment period followed by a maintenance period ranging from 32 to 40 weeks. In BE READY, BE VIVID, and BE SURE, co-primary endpoints were measured at week 16 and included:

- a PASI 90 response in BE READY, BE VIVID, BE- SURE and
- an investigator's global assessment response (IGA) 0/1 response (represented by an IGA score of 'clear' (0) or 'almost clear' (1)) with at least a two-category improvement from baseline.

In BE RADIANT, the primary endpoint was a PASI 100 response at week 16.

Treatment regimens and comparators differed between the trials as follows:

- **BE READY** (77 sites; 9 countries): 435 patients were randomised 4:1 to receive **bimekizumab 320 mg every 4 weeks (Q4W)** or **placebo** for 16 weeks. Patients on bimekizumab with a week 16 PASI 90 response entered a 40-week randomised withdrawal phase and were re-randomised 1:1:1 to bimekizumab 320 mg Q4W or bimekizumab 320 mg every 8 weeks (Q8W) or placebo. Patients without a response at week 16 or who relapsed during the withdrawal phase (relapse defined as no longer achieving a PASI 75 response at Week 20 or later) were eligible to enter an open label bimekizumab 320 mg Q4W 'escape' arm. Week 16 responders initially randomised to placebo remain on placebo after the initial treatment period.
- **BE VIVID** (105 sites; 11 countries): 567 patients were randomised 4:2:1 to receive **bimekizumab 320 mg Q4W, ustekinumab 45/90 mg every 12 weeks (Q12W)** or **placebo** for 16 weeks followed by a 36-week maintenance period. At week 16, patients on placebo switched to bimekizumab 320 mg Q4W.
- **BE SURE** (77 sites; 10 countries): 478 patients were randomised 1:1:1 to receive **bimekizumab 320 mg Q4W; bimekizumab 320 mg Q4W**, switching to Q8W from Week 16; or **adalimumab 40 mg every 2 weeks (Q2W)**, switching to bimekizumab 320 mg Q4W at Week 24.
- **BE RADIANT** (77 sites; 11 countries): 743 patients were randomised 1:1 to receive **bimekizumab 320 mg Q4W** or **secukinumab 300mg Q4W**. At Week 16, patients were randomised 1:2 to receive bimekizumab 320 mg Q4W or Q8W. At the end of the 48-week double blind period, patients could enter a 96-week open label extension period.

Patients completing the randomised withdrawal phase or escape arm of BE READY or the maintenance phase of BE- SURE or BE VIVID were eligible to take part in a 144-week open-label extension study (BE BRIGHT) to assess the long-term safety, tolerability and efficacy of bimekizumab. Only safety data from BE BRIGHT are included as part of a pooled safety evaluation in the current submission. In response to clarification question A7, the company report that final results from BE BRIGHT are expected in mid-2023 and that interim efficacy and safety results (from a data lock at June 2020) are available on request. Patients not entering BE BRIGHT had a safety follow up 20 weeks after their final dose in their original trial.

3.1.3 Key efficacy results from pivotal trials

The CS is primarily based on evidence of clinical effectiveness for bimekizumab during the initial 16-week treatment period of the pivotal trials. Key results from these trials are as follows:

- Bimekizumab Q4W achieved [redacted] for the PASI 90 co-primary endpoint at week 16 compared to placebo [redacted] ustekinumab ([redacted]) and adalimumab ([redacted]) in BE READY, BE VIVID and BE SURE (CS Figure 8; all p values <0.001 for superiority).
- Bimekizumab Q4W achieved a [redacted] in BE RADIANT (primary endpoint) compared to secukinumab [redacted] (CS Figure 9; p<0.001 for superiority).
- IGA 0/1 response rates were also higher for bimekizumab Q4W compared to placebo, ustekinumab and adalimumab (p<0.001 for superiority) in BE READY, BE VIVID and BE SURE; [redacted] (CS Section B.3.6.2 and CS Appendix K).

Key results across the four pivotal trials for the less stringent PASI 75 response measure are as follow:

- Bimekizumab Q4W achieved [redacted] response rates at week 16 (ranging from [redacted] to 95.4%) compared to placebo (2.3% to [redacted]%), ustekinumab [redacted] and adalimumab (69.2%), [redacted]).
- The PASI 75 response rate was also higher for bimekizumab Q4W at week 4 (after a single dose) compared to all trial comparators (pre-specified secondary endpoint; all [redacted] for superiority; CS Figure 10).

Key results from the maintenance periods from the bimekizumab trials are as follows:

- Supporting evidence of [redacted]) in BE VIVID, BE SURE and BE RADIANT (CS Figures 12-14).
- A pooled analysis of BE READY, BE VIVID and BE SURE showed that a [redacted]

[redacted] with PASI 90, PASI 100 and IGA 0/1 responses at week 16 maintained the response at week 52 (CS Table 19).

- In BE READY, the relapse rate at week 56 (defined as not achieving a PASI 75 response at Week 20 or later) of patients who had a PASI 90 response at week 16 and who entered the randomised withdrawal phase was [redacted] for the bimekizumab Q4W arm and [redacted] for the bimekizumab Q8W arm compared to [redacted] for the placebo arm (CS section B.3.6.3). Time to relapse was not reported.

The ERG notes that results from the trial maintenance periods are not used in the economic modelling or in the NMA. The company consider that the data from the initial 16-week treatment period are most relevant for decision making, in keeping with previous NICE appraisals in this topic area (clarification response A16). They also explain that the different design features during the maintenance periods in the trials across the evidence base (lack of placebo control, different inclusion criteria, different doses etc) would lead to data challenges if an NMA were performed. The ERG agrees that the company's focus on the initial treatment period is consistent with previous NICE appraisals.

Results for other endpoints measured in the trials include PASI 50, symptoms of psoriasis (itch, pain and scaling), scalp IGA, palmoplantar IGA (pp-IGA), modified Nail Psoriasis Severity Index (mNAPSI) and the disease-specific quality of life measure Dermatology Life Quality Index (DLQI) (CS section 3.6.2 and Appendix K).

Pre-specified sub-group analyses for data pooled from BE READY AND BE VIVID are included in CS Appendix E for the subgroups listed in the NICE scope. PASI 90, PASI 100 and IGA 0/1 response rates [redacted]

3.2 Critique of the clinical effectiveness evidence submitted

3.2.1 Company searches for clinical evidence

The company's searches for clinical effectiveness evidence were initially performed up to 5th March 2019 and updated on 1st July 2020 (CS Appendices D.1.1 and D.1.2). Studies of all relevant systemic therapies (non-biologic and biologic) were included which is consistent with the NICE scope but broader than the company's decision problem which focuses on selected

biologics. The search identified a total of 84 studies for inclusion in a network meta-analysis (see section 3.4 below) including the 4 pivotal phase III RCTs of bimekizumab. The ERG considers the searches and selection criteria to be appropriate and do not believe any relevant published trials were excluded.

3.2.2 Internal validity of bimekizumab trials

The company assessed the four bimekizumab RCTs as having a low overall risk of bias (CS section B.3.5 and Appendix D.3) according to the NICE quality appraisal checklist. The ERG agrees. Discontinuation rates were generally low at week 16 (around 3-6% of randomised patients, CS Appendix D.2) except in the placebo arm of BE VIVID (10.8%). Reported baseline characteristics were well balanced between trial arms with the exception that a [redacted] of patients in the BE READY placebo arm had [redacted] than in the bimekizumab arm. The ERG's clinical expert is of the opinion that [redacted]

A fixed hierarchical statistical testing sequence was adopted in each of the four trials (CS Table and Appendix I.3). Bimekizumab was tested for superiority against placebo in BE READY and BE VIVID for the co-primary endpoints. Testing for superiority against active comparators in BE VIVID, BE SURE and BE RADIANT only proceeded when non-inferiority had been demonstrated for the primary co-endpoints. Planned sample sizes were reached (CS Table 13). The ERG considers the statistical methods to be appropriate.

The ERG considers the trials to be well designed and executed, with overall low risk of bias.

3.2.3 External validity of bimekizumab trials

The majority of patients in the four pivotal bimekizumab trials were Caucasian ([redacted], CS Tables 10 and 11[redacted]. The ERG notes that UK patients represented less than [redacted] of the four trial populations. [1-4]

The mean age (ranging from [redacted]) and BMI ([redacted]) of participants across the four trials were consistent with that observed in a real-world registry of adults with chronic plaque psoriasis treated with biologics in the UK (British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR); CS Figure 6). The trial populations had lower DLQI scores ([redacted]) than patients in the BADBIR register (approximately 17) despite a slightly higher PASI score ([redacted] compared to approximately 16) and a higher proportion of patients with comorbid psoriatic arthritis ([redacted] compared to approximately 22%). The trial populations also comprised more males ([redacted] than the BADBIR population (around 61%). The ERG's clinical expert considers that the trial populations are relatively similar and any differences are unlikely to impact response.

The trial populations represent a broader population than the company's decision problem (see section 2.1 of this report) and could therefore potentially include patients using bimekizumab as first-line systemic therapy (i.e. naïve to non-biologic systemic therapies), as well as patients previously in receipt of systemic therapy. The proportion of patients who had previously used any systemic therapy ranged from [redacted] and the proportion who had previously used any biologic therapy ranged from [redacted].

The bimekizumab trial populations were comparable with the trial populations for the company's cost-comparators (risankizumab, ixekizumab and brodalumab) with respect to age, sex and disease duration (CS Appendix D.1.4 Table 11). One exception was the trial population of the SustaIMM phase II/III trial comparing risankizumab and placebo in Japanese patients comprising slightly older patients and a higher proportion of male patients. [5] The proportion of patients who had used prior biologic therapy varied more widely across the cost-comparator trials (7.9% to 46%; CS Appendix D.1.4 Table 11) which may reflect changing practice over time.

3.3 Critique of the evidence on safety submitted by the company

Safety data were pooled from the bimekizumab clinical trial programme as follows:

- Pool S1 included data from the initial treatment period (weeks 0-16) of the placebo-controlled trials, BE READY and BE VIVID. Data were considered for bimekizumab and placebo arms only; patients who were randomised to ustekinumab in BE VIVID were not included in this safety analysis.
- Pool S2 included data from the initial treatment, maintenance and open-label extension periods for all bimekizumab doses all Phase II and Phase III bimekizumab trials, except

BE RADIANT as this study was still blinded at the time of pooling. Safety data for adalimumab and ustekinumab from BE SURE and BE VIVID were also included in Pool S2 for the purposes of comparison with the pooled bimekizumab safety data. However, the CS presents Pool S2 safety data for the bimekizumab trial arms only.

3.3.1 Safety data pooled from all Phase II and Phase III bimekizumab trials

Pooled adverse event frequencies for the bimekizumab arms only from trials in Pool S2 (N=[redacted]; CS section B.3.10 and Appendix F) are as follows:

- [redacted]% of patients in Pool S2 reported one or more treatment emergent adverse event (TEAEs).
- The most frequent TEAEs were reported within [redacted]
- [redacted]% of patients had a treatment-related TEAEs (as assessed by investigator); [redacted] was the most frequently reported treatment-related TEAE ([redacted]%).
- Pre-specified AESI were reported [redacted] (CS section 3.10.2).
- [redacted]% of patients reported a serious TEAE and [redacted]% discontinued treatment due to TEAE(s)
- The CS does not report the number of serious TEAEs assessed as related to bimekizumab, however, [redacted].

3.3.2 Comparative safety for bimekizumab versus placebo

Pooled adverse event frequencies for bimekizumab compared to placebo from Pool S1 (N=[redacted]; CS Appendix F) are as follows:

- A [redacted] proportion of patients receiving bimekizumab Q4W experienced one or more TEAE compared to placebo ([redacted]% versus [redacted]% respectively).
- Treatment-related TEAEs were [redacted] in patients receiving bimekizumab Q4W compared to placebo ([redacted]% versus [redacted]%).

- [redacted]
- [redacted] of patients receiving bimekizumab Q4W [redacted] and [redacted] in the bimekizumab Q4W group ([redacted]%)
- [redacted].

3.3.3 Comparative safety for bimekizumab versus active comparators

Adverse event frequencies for bimekizumab compared with each respective active comparator in BE VIVID (ustekinumab), BE SURE (adalimumab) and BE RADIANT (secukinumab):

- Overall incidences of TEAEs were [redacted] during the initial treatment periods and across both initial treatment and maintenance periods in these three studies (for details see CS Appendix F,11 to F.1.3 Tables 17 to 21).
- [redacted].
- Treatment-related TEAEs were [redacted] in bimekizumab trial arms (ranging from [redacted] compared to respective active comparators (ranging from [redacted]). The CS reports that this is likely driven by a higher frequency of fungal infections in patients receiving bimekizumab. The majority of cases of oral candidiasis across all four pivotal trials were mild to moderate [redacted], managed with standard anti-fungal therapy and did not lead to treatment discontinuation (CS Table 25).

3.3.4 Comparative safety for bimekizumab versus cost comparators

Network meta-analyses were conducted to compare frequencies of serious AEs and AEs leading to treatment discontinuation between bimekizumab and the company's selected cost comparators (CS Figures 18 and 19). The results of these NMAs are further discussed in the next section of this report (section 3.4).

3.4 Critique of the Network Meta-Analysis (NMA) submitted by the company

The pivotal phase III bimekizumab RCTs did not include any of the three biologic drugs selected for cost comparison in the decision problem. Thus, an indirect comparison was required to assess similarity between bimekizumab and these biologics. As we noted earlier, cost-comparison analyses have informed the appraisals of two NICE- recommended biologic drugs in this indication (risankizumab and guselkumab). In both appraisals, the assumption of similarity in efficacy and safety was informed by network meta-analyses (NMA). Likewise, NMA is the company's chosen approach for demonstrating similarity of bimekizumab to existing approved biologic drugs. Where possible we critique their NMA in terms of consistency with NMA assumptions and data considered acceptable in the previous cost-comparison appraisals.

The indirect treatment comparison (NMA) presented in the CS comprises RCTs, identified by the literature search undertaken for the company's systematic review of clinical effectiveness. NMAs are reported for one efficacy outcome measure and two safety measures:

- Efficacy
    - PASI – patients achieving 50%, 75%, 90% and 100% improvement in PASI at 10-16 weeks. (n=84 RCTs)
- Safety
    - Serious adverse events (AEs) at 10-16 weeks (n=84 RCTs)
    - Discontinuation due to adverse events (AEs) at 10-16 weeks (n=86RCTs)

These outcome measures directly inform the cost comparison analysis (NB. Of the four PASI categories only PASI 75 informs the efficacy analysis). The ERG notes that an NMA of the DLQI outcome was not reported in the CS, despite this outcome being included in the NMAs included in previous appraisals (TA521 guselkumub; TA596 risankizumab). Based on the results of the bimekizumab phase III RCTs and information available from previous appraisals, the ERG's observation is that, based on the DLQI, bimekizumab appears to be as efficacious as the other biologics in terms of health-related quality of life.

3.4.1 Inclusion criteria for the NMA

As mentioned earlier, the inclusion criteria for the company's systematic review of clinical effectiveness, whilst matching the NICE scope, was broader than the decision problem. The

evidence network therefore includes studies of biologic drugs and systemic non-biologic drugs (e.g. methotrexate, cyclosporine). The presentation of the NMA results, however, focuses on the comparisons relevant to the decision problem (i.e. only comparisons between biologics). The reason for including non-decision problem treatments in the network is not explicitly reported in the CS. The ERG therefore assumes their role is to provide additional evidence to the network to strengthen the relevant comparisons between bimekizumab and the other biologics. We consider these trials provides the network with slightly greater strength in terms of connectivity, with the caveat that this has the potential to increase heterogeneity (see section 3.4.4).

3.4.2 Quality assessment of trials in the NMA

In response to clarification question A8a, the company confirmed they had used the Cochrane Collaboration's Risk of Bias (RoB-2) tool to assess five individual risk of bias domains and an overall risk of bias judgement for each trial in the NMA. (CS Appendix D.1.7). Most studies (69/84) were assessed as having low risk of bias overall (CS section B.3.9.4). No sensitivity analyses were conducted to assess the impact of studies with 'some concerns' (10/84) or high risk of bias (5/84). The company comment that the main driver of bias was missing data (due to lack of ITT analysis). No narrative is provided in the CS to justify the company's judgments, and it is unclear how the overall judgement of bias for each study was derived from the individual domain assessments. It was not practical for the ERG to perform an independent appraisal of the 84 trials but we consider the company's critical appraisal methods overall to be appropriate.

3.4.3 NMA modelling approaches

The CS reports using two different statistical modelling approaches their NMA, both based on methods recommended by the NICE Decision Support Unit (DSU):

- A Bayesian multinomial likelihood model using a probit link to estimate PASI response (based on NICE DSU Technical Support Documents (TSD) 2,3 and 5).
- A Bayesian logit model to estimate serious AEs and discontinuations due to AEs (based on NICE DSU TSD2).

The Bayesian multinomial probit regression model (we also refer to this as the 'standard model') was used to simultaneously model treatment response across the PASI-50, 75, 90, and

100 categories. The ERG agrees this is the optimal NMA approach for correlated data such as PASI response. Variations to this model were explored in respect of two key assumptions:

1. **Proportional treatment effects.** The standard model retains the same ranking for each treatment across each PASI-response category. Additionally, the company produced a model which relaxed this assumption - the "REZ" multinomial probit model. They suggest that relaxing this assumption is more realistic, less restrictive, and is supported by empirical evidence of modest variability in treatment rankings when separate binomial analyses were conducted for PASI 75, 90 and 100. The company also notes that the REZ model was consistently a better fit compared to the standard multinomial probit model, which may suggest a violation of the proportional treatment effect assumption in the latter. Although the REZ model does not appear to have been used in previous NICE appraisals of biologics for plaque psoriasis, the ERG considers the company's justification for its inclusion in their NMA is reasonable. We encourage the company to fully publish this model in order it can be considered in any future appraisals in this indication.
2. **Baseline risk**. The company suggests that in autoimmune diseases the placebo rate and the relative effect of a treatment versus placebo in a trial are likely to be related, necessitating an adjustment for baseline placebo risk. They note that adjustments have been included in the NMAs used in the two previous cost comparison appraisals in psoriasis (TA596 risankizumab, TA521 guselkumab). The company's *A priori* preference, therefore, was to adjust for baseline risk.

For PASI response a total of eight models were run, based on different combinations of the above assumptions plus assumptions about whether random effects or a fixed effect applies (**Error! Reference source not found.**).

Table 1 Summary of PASI NMA Bayesian multinomial probit modelling assumptions

Model		
Proportional treatment effects	**Baseline risk**	**Effects**
Relaxation of assumption allowed ("REZ model")	Adjusted	Fixed effect
		Random effects (base case)
	Unadjusted	Fixed effect
		Random effects
Standard assumption	Adjusted	Fixed effect
		Random effects
	Unadjusted	Fixed effect

		Random effects

Source: based on CS Table 22.

The best-fitting models, in terms of lowest deviance information criteria (DIC) value, were those which did not adjust for baseline risk (CS Table 22). However, as stated above, the company's preference was to adjust for baseline risk and to maintain consistency with previous cost comparison appraisals (TA521 guselkumab; TA596 risankizumab). Hence, the REZ multinomial probit model adjusted for baseline risk which had the next lowest DIC (i.e. the next best fit) with random effects was chosen as the base case model (indicated in **Error! Reference source not found.** by blue shading). The ERG concurs with the company's preference for random effects given the large quantity of studies and thus the increased likelihood of heterogeneity (see section 3.4.4).

Scenario analyses explored various combinations of alternative assumptions about proportional/non-proportional treatment effects, random effects/fixed effect, and unadjusted/non-adjustments for baseline risk.

For the safety NMA the binomial logit models assuming random effects and a fixed effect yielded similar DIC values, respectively. Given the large number of studies included in the network, and thus the potential for increased heterogeneity, the company opted for random effects in their base case. The ERG agrees that this decision is appropriate.

3.4.4 Heterogeneity assessment

In such a large network of trials there is inevitable heterogeneity, and a potential for an imbalance of the distribution of treatment effect modifiers of most concern in terms of bias. However, the company argues there is no consensus on treatment effect modifiers in plaque psoriasis trials, although prior biologic use has been hypothesised as a treatment effect modifier (clarification question A9).

Expert opinion to the ERG suggests that, in patients who switch biologic treatments, response to subsequent biologic treatments may be lower than the level of response achieved by the initial biologic therapy. The size of the response to a subsequent biologic depends on whether there was non-response to the previous biologic (primary failure – in which case a the patient might switch to a biologic with a different mode of action) or whether response was achieved but lost

over time (secondary failure – in which case a patient might switch to a biologic with a different mode of action, or an alternative biologic with similar mode of action).

The company notes that there was no statistical interaction effect in subgroup analysis on prior use of biologics therapy in the bimekizumab phase III RCTs trials. Their view is that, in the absence of evidence to the contra, prior biologic treatment is assumed not to be a treatment effect modifier. The ERG notes that trial subgroup analyses are not statistically powered to identify treatment interactions and therefore a significant treatment-subgroup interaction cannot necessarily be ruled out.

The CS reports that prior use of a biologic use varied between 0% to 39% of patients in the trials included in the NMA. However, this is not fully informative without knowing the mean or median, nor the proportion of patients who had received multiple biologics, nor if trials of certain biologics had higher proportions of patients with prior biologic use (as might be the case for newer treatments). The ERG notes that the proportion of patients in the bimekizumab phase III RCTs who had previously used biologics was in the range [redacted], thus at the upper end of the range for the network as a whole.

Given the relatively large number of trials in the network the ERG presumes that meta-regression would have been feasible to explore the impact of prior biologic use and other patient and study characteristics. The company argues that adjustments they made for baseline placebo risk (as described below) account for heterogeneity between the trials to some extent. The ERG notes that, whilst this may be the case, it cannot necessarily be assumed that the risk of bias has been removed. Nonetheless, given that the proportion of patients with prior biologic use in the bimekizumab trials was at the higher end of the range for the network as a whole, and if it is accepted that response to subsequent biologics may not be as high as the initial biologic, then the results of the NMA are not likely to be biased in favour of bimekizumab.

3.4.5 NMA data and statistical procedures

The effect estimates from each trial that were used in the NMA were not reported in the submission, but data formatted for the analysis was provided alongside model programming code following ERG request (clarification question responses A12-14). It was not practical for the ERG to cross-check the data against the 84 source trials for accuracy.

The CS states that data from the intention-to-treat (ITT) population of all included studies informed the NMA. However, the ERG is unclear which, if any, outcome data has been imputed by the company. The CS states "NRI [non-responder imputation] data was used as the preferred imputation method for accounting for missing PASI outcome data" (CS p80). However, clarification question responses A12 and A14 state that the company did not impute any data in the base case REZ model and the baseline risk adjusted models. Further, the data provided for the standard model matches that of REZ model hence the ERG remains unclear what, if any, imputation was made by the company.

The ERG validated the company's standard multinomial probit code against the code in NICE DSU TSD2 and was satisfied the REZ model (which is based on the standard multinomial probit code) had been reasonably implemented. The company used a number of semi-informative priors in the REZ model. These priors did not affect model fit (clarification question response A18) however any impact these may have had on treatment effects is uncertain.

3.4.6 NMA results

The base case results were consistent across the scenario analyses including the REZ fixed effect model (CS Appendix D, Figure 5), models without baseline adjustment (CS Appendix D, Figures 6 & 7), and the standard random effects multinomial probit model (CS Appendix D, Figure 8).

In the NMA of safety outcomes [redacted] (CS, Figures 18, 19).

3.4.7 Consistency of NMA results with other evidence

Parity between bimekizumab and the comparator biologics, as suggested by the results of the NMA, is supported by direct evidence from the bimekizumab trials, NMA results from previous appraisals, and clinical opinion.

As reported earlier (section 3.1) head-to-head comparisons of bimekizumab versus adalimumab, secukinumab, and ustekinumab from the phase III bimekizumab trials showed that bimekizumab had similar or better PASI response rates in relation to these comparators.

Analyses informing previous appraisals have also suggested similar efficacy between biologics. Risankizumab was comparable to guselkumab, and equal or better compared to other biologics across PASI-response categories (TA596). Similarly, guselkumab had comparable (non-statistically significant differences) PASI-90 and PASI-75 responses to those of ixekizumab, secukinumab, ustekinumab, infliximab, adalimumab, and guselkumab (TA521 committee papers, company submission, Table 14).

The assertion of comparable safety is supported by evidence of a similar safety profile between bimekizumab and comparator biologics in the head-to-head bimekizumab phase III trials (CS Appendix D, tables 17, 19 & 20; section 3.3 of this report). Likewise, similar safety profiles amongst the biologics were reported in the guselkumab and risankizumab appraisals

Expert clinical opinion to the ERG also concurs that the assumption of similar efficacy and safety for bimekizumab is reasonable.

3.4.8 Consistency of placebo efficacy and safety outcomes in biologics trials

The ERG assessed the consistency of the placebo arm PASI response and safety outcomes from the bimekizumab phase III trials with those reported by trials of the other biologics.

CS Appendix D.1.4, Figure 2 shows that the placebo response rate for PASI 75 at the end of the initial treatment period ranged from 0 to 18.9% across the placebo arms of the trials included in

the NMA, with most trials reporting a placebo response rate <10%. (NB. The ERG notes that the BE-ABLE study, a phase IIb bimekizumab RCT is included in this Figure but is not included in the NMA). The placebo response rate for PASI 75 ranged from 2.3-7.2% in the bimekizumab trials (BE READY and BE VIVID) and was similar to that observed in key pivotal trials used to support NICE submissions for the cost comparator drugs (risankizumab: 8.2 to 9.8%; brodalumab: 2.7-8.1%; ixekizumab: 2.4-7.3%). [6-8] Smaller placebo response rates were observed in the bimekizumab trials for PASI 90 (1.2-4.8%) and PASI 100 (0.0-1.2%) and for SAEs [redacted]){UCB Pharma Ltd, 2020 #68} which were [redacted] with those observed for the cost comparator trials. [6-8]Discontinuations due to AEs were [redacted] in the placebo arms of the bimekizumab trials ([redacted]%) compared to the cost comparator trials (ranging from 0.3 to 3.9%). The ERG's conclusion, based on the evidence available, is that the bimekizumab trial placebo efficacy and safety outcomes are not discordant with those of the trials of other biologics for plaque psoriasis.

3.5 ERG conclusions on the clinical effectiveness evidence

- The clinical effectiveness evidence for bimekizumab is from a series of large multinational phase III RCTs. The trials have compared bimekizumab with placebo and three biologic treatments: adalimumab, ustekinumab and secukinumab. Although these comparator treatments are still considered standard practice in the management of plaque psoriasis, a number of newer biologic drugs have been recommended by NICE since the trials were initiated.
- The trials appear well designed and executed, with overall low risk of bias. Statistical hypotheses included demonstrating non-inferiority and then superiority of bimekizumab to comparators.
- The bimekizumab trial populations were comparable with the trial populations for the company's cost-comparators (risankizumab, ixekizumab and brodalumab), and appear generalisable to patients treated within the NHS. The bimekizumab trial populations represent a broader population than that defined in the company's decision problem.
- The company's NMA is informed by a comprehensive systematic literature review. The ERG considers the review to be low risk of bias and is unlikely to have omitted any relevant key studies.
- The inclusion criteria for the NMA is broader than the decision problem, and consequently the network includes a proportion of trials of systemic non-biologic treatments. Appropriately, however, the results of comparisons of bimekizumab versus systemic non-

biologics are not presented. The ERG's assumption is that trials of systemic non-biologics are included to strengthen connections within the network by increasing the number of patients contributing outcome data. Whilst this might be beneficial for boosting statistical power, a limitation is that it may also increase heterogeneity.

- The NMA modelling approaches are appropriate, based on NICE DSU recommended methodology. Reporting of methodology and statistical procedures is generally good.
- The company's base case NMA model (the REZ model) uses an alternative assumption about proportional treatment effects (i.e. that the ranking of the treatments in probability of PASI response is not necessarily the same across each of the four PASI-response categories) not featured in previous appraisals of biologics in plaque psoriasis. However, the ERG considers the company's justification for this model to be reasonable. The NMA results are consistent across a comprehensive set of scenario analyses, demonstrating robustness to modelling assumptions.
- The ERG notes heterogeneity in some baseline patient characteristics across the trials, particularly prior biologic treatment experience, a hypothesised treatment effect modifier. The CS reports that between 0-39% of patients across the trials had previous biologic experience. A similar proportion of patients in the bimekizumab trials were biologic experienced. If it is assumed that response to a biologic treatment (in this case bimekizumab) might be lower for patients who had an inadequate response/loss of response to a previous biologic, then, in the ERG's opinion, any bias from heterogeneity in the NMA is not likely to favour bimekizumab.
- Based on the robust results of the company's NMA, and the consistency of these results with those from previous NICE appraisals, the ERG considers the assertion of similarity in efficacy and safety between bimekizumab versus other biologics to be acceptable.

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

4.1 Decision problem for cost comparison

4.1.1 Population

We discuss the company's specification of the population for the decision problem in section 2.1 above. The ERG agrees that the population for the cost-comparison analysis should reflect that in NICE recommendations for the comparators. In practice, the cost analysis uses input parameters estimated from trials with a broader population:

- The modelled cohort has a mean age of 45.1 years, with 69% male (CS Tables 10 and 11), based on the pooled ITT populations of the bimekizumab RCTs BE READY, BE SURE, BE VIVID, and BE RADIANT trials. These demographics are consistent with models for comparator appraisals (TA596 AbbVie submission for risankizumab Table 21; TA511 for brodalumab Leo Pharma submission Table 56; and TA442 for ixekizumab Eli Lilly submission Table 90); and with other trials in the company's NMA (CS Appendix D Table 11). In the model, population demographics only affect mortality rates, which has little impact on cost estimates (CS Table 31).
- The key clinical input in the model (the probability of a PASI-75 response after the initial induction period) comes from the company's base case NMA (CS Appendix D.1.8 Table 13). Limited subgroup analyses by baseline psoriasis severity and prior therapy experience are available for bimekizumab versus placebo from the BE READY and BE VIVID trials (CS Appendix E). This found [redacted].

Similar issues have arisen in previous NICE appraisals, and committees have concluded that the trial populations are generalisable to the target population of NHS patients who meet existing criteria for access to biologics. For example, see section 3.5 in the brodalumab guidance (TA511) and paragraphs 4.5, 4.6 and 4.8 in the ixekizumab guidance (TA442).

4.1.2 Comparators

The analysis compares bimekizumab with brodalumab, ixekizumab and risankizumab. As stated in section 2.2 above, the ERG considers that these comparators are appropriate for a cost-comparison.

4.2 Cost-comparison model

The company describes their cost-comparison model in CS section B.4.2.1. The model structure is illustrated in CS Figure 20. The model structure and key assumptions are consistent with previous cost-comparisons for risankizumab and guselkumab (TA596 and TA521), and there are shared features with other appraisals of biologics for adults with moderate to severe psoriasis. See CS section B.2 and Table 5 for the company's summary of key clinical features of prior appraisals. See CS Table 27 for a summary of the parameter values in the company's base case and scenario analyses. We discuss these inputs below.

4.3 Model parameters

4.3.1 Induction response

In the base case costing model, the company sets the PASI 75 response probabilities for the included comparators (ixekizumab, risankizumab and brodalumab) equal to the bimekizumab estimate of [redacted] from their preferred NMA analysis [redacted] (CS Appendix D.1.8 Table 13).

[redacted]

[redacted] It is therefore important to consider the robustness of the NMA, and other factors, such as pharmacological similarity when judging the appropriateness of the cost-comparison assumption.

The company present sensitivity analysis for the PASI 75 response rate based on the credible interval [redacted] (CS Figures 21-23). We extend this range to further explore uncertainty over this parameter (from [redacted]).

4.3.2 Discontinuation

An equal probability of 20% discontinuation per year was assumed across all the treatment arms. This is consistent with previous cost-comparisons TA596 and TA521. The company vary this rate in sensitivity analysis by -/+ 20% (16% to 24% annual discontinuation). They also test scenarios with discontinuation rates from alternative sources, as in the TA596 risankizumab cost-comparison: Warren et al. 2015 (11%); TA511 (18.7%); and Egeberg et al. 2018 (19%).[9-11]

4.3.3 Mortality

The model uses general population mortality rates, adjusted for the age and sex of the modelled cohort (England and Wales 2017-2019, ONS 2020).

In the brodalumab appraisal (TA511), the committee concluded that adjustment for the increased risk of death in patients with moderate to severe psoriasis was appropriate (UK GPRD study hazard ratio 1.42, 95% confidence interval 1.25 to 1.62). They noted that the increased risk was likely to be related to co-morbid conditions associated with severe plaque psoriasis, and that treating psoriasis would not extend life.

The company test the impact of excluding mortality in scenario analysis (CS Table 31). We also test the impact of including the mortality hazard ratio (1.42) from TA511.

4.3.4 Costs

The company set out the dosing assumptions and list prices for the calculation of acquisition costs for bimekizumab and comparators in CS Table 26. We summarise the key assumptions in Table 2 below.

Table 2 Dosing and list prices for bimekizumab and comparators

Therapy (dose)	Induction		Maintenance (doses per year)	List price per dose
	Duration	Doses		
Bimekizumab (2 x 160 mg)	16 weeks	5	6.5	[redacted]
Brodalumab (1 x 210 mg)	12 weeks	8	26.0	£640.00
Ixekizumab (1 x 80 mg)	12 weeks	8	13.0	£1,125.00
Risankizumab (2 x 75 mg)	16 weeks	3	4.3	£3,326.09

See confidential addendum to ERG report for comparator PAS prices and analyses

The usual maintenance dose for bimekizumab is 320 mg once every 8 weeks. CS Table 2 notes that:

[redacted]." In response to clarification question B1, the company further explains that

[redacted]

[redacted]

The ERG acknowledges these points.

[redacted]

The company exclude administration and monitoring costs from their cost-comparison analysis (see CS B.4.2.3). They note that administration costs were not included in costings for NICE appraisals of other subcutaneously administered biologics, including the comparators brodalumab, ixekizumab and risankizumab. The clinical expert consulted by the ERG, agreed that self-administration of subcutaneous injections with pre-filled pens is simple, and would not differ for bimekizumab and comparators. Administration is supported by NHS resource at the first injection in clinic, and by company provided home delivery and support (or remote consultation by video because of current COVID-19 restrictions). The ERG therefore agrees that there is no need to include treatment administration costs in the cost-comparison.

We also agree with the exclusion of monitoring costs from the cost-comparison. The expert who we consulted noted that monitoring usually consists of an assessment at 12-16 weeks, with 6/12 monthly routine clinic follow-up. However, monitoring tests are not onerous, and do not differ between biologics. Patients who experience a loss of response on maintenance treatment would usually have a clinic review for assessment and consideration for alternative treatment.

However, as the rate of discontinuation is assumed to be the same for bimekizumab and comparators, the cost of treatment-switching would be similar, so does not need to be included in the cost model.

The company also excluded costs for treatment of adverse events (CS B.4.2.4). They explain that the NMAs of serious AEs and discontinuation due to AEs found [redacted] (CS B.3.10.2). The company note higher rates of fungal infections with bimekizumab, but argue that these are mostly mild or moderate, with minimal costs. The ERG's clinical expert agreed that biologic treatments for psoriasis are generally well tolerated, and that adverse event rates are unlikely to differ between treatments.

4.4 ERG model checks

The ERG conducted a range of checks on the company's cost-comparison model. This included verification that all input parameters and model results matched the values cited in the CS and, where available, values in published sources. We also inspected formulae in the Markov trace and intermediate calculations ('white box' verification) and checked that changes to input parameters had a plausible impact on results ('black box' verification).

We identified the following minor issues, neither of which affected the results:

- There are small discrepancies in the sum of the number of patients in the health state traces for bimekizumab, ixekizumab and risankizumab: they do not add up to 1. However, these do not impact on the results.
- Errors in cells L89:089; N90; O90; and O91 in Sheet!Mortality Inputs. These were corrected but made no difference in the overall model results (because they do not apply within the modelled time horizon).

4.5 Cost comparison analysis results

The company base case cost comparison results at list prices are presented in CS Table 29 and at PAS price are in CS Table 30. We note, however, that these analyses do not take account of PAS discounts for comparators. Uncertainty over model assumptions was assessed with one-way sensitivity analyses (presented in CS Figures 21-23) and scenario analyses (CS Table 31).

4.6 ERG analysis

We summarise the results of the company's base case, sensitivity analyses and scenario analyses at list price in Table 3 and Table 4 below. In line with NICE methodological guidance for FTA cost-comparisons, the company did not report a probabilistic sensitivity analysis. All results are therefore deterministic.

In addition to the company's sensitivity and scenario analyses, Table 4 includes the following ERG scenarios:

- A wider range for the PASI 75 response probabilities ([redacted]) to further explore sensitivity to this parameter.
- A 20-year time horizon.
- Mortality multiplier for moderate to severe psoriasis compared with general population (hazard ratio 1.42 from TA511).
- [redacted]

All of these results indicate that bimekizumab is more costly than the comparators when all treatments are costed at list price. We show results with NHS price discounts for bimekizumab and the comparators in a separate confidential addendum to this report.

Table 3 Company's base case results – list price for bimekizumab and comparators

Therapy	Total cost over 10 years	Cost difference: bimekizumab minus comparator
Bimekizumab	[redacted]	
Brodalumab	£65,769.52	[redacted]
Ixekizumab	£62,304.35	[redacted]
Risankizumab	£62,384.76	[redacted]

Source: Results produced by ERG from the company's model, and CS Table 29

Table 4 ERG's sensitivity and scenario analyses – list price for bimekizumab and comparators

Scenario		Cost difference: bimekizumab minus comparator		
		Brodalumab	Ixekizumab	Risankizumab
Base case		[redacted]	[redacted]	[redacted]
PASI 75 response (*base case* [redacted])	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted] (lower CrI)	[redacted]	[redacted]	[redacted]
	[redacted] (upper CrI)	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation (*base case 20%*)	11% (Warren 2015)[11]	[redacted]	[redacted]	[redacted]
	16% (-20%)	[redacted]	[redacted]	[redacted]
	18.7% (TA511)	[redacted]	[redacted]	[redacted]
	19% (Egeberg 2018)[9]	[redacted]	[redacted]	[redacted]
	24% (+20%)	[redacted]	[redacted]	[redacted]
Time horizon (*base case 10 years*)	5 years	[redacted]	[redacted]	[redacted]
	20 years	[redacted]	[redacted]	[redacted]
Discount rate (0%)	3.5% per year	[redacted]	[redacted]	[redacted]
Mortality *(base case general population)*	Exclude mortality	[redacted]	[redacted]	[redacted]
	Multiplier 1.42 (TA511)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Results produced by ERG from the company's model.

[redacted]

4.7 ERG conclusions on cost comparison

- The structure and key assumptions of the company's cost-comparison model are appropriate, and consistent with previous cost-comparison appraisals (risankizumab TA596 and guselkumab TA521) and with economic analyses in other appraisals (ixekizumab TA442 and brodalumab TA511). We did not identify any important errors in the model coding.
- Results of the company's NMA suggest that

  [redacted]

  This supports the assumption of similar efficacy, although this may over-estimate costs for the comparators. It is therefore important to consider the robustness of the NMA,

and other factors, such as pharmacological similarity when judging the appropriateness of the cost-comparison assumption.

- With list prices for all treatments, bimekizumab is estimated to be more costly than the comparators risankizumab, ixekizumab and brodalumab. This applies for the company's base case analysis and for all company and ERG sensitivity and scenario analyses. Results with PAS discounts for bimekizumab and comparators are shown in a confidential addendum to this report.
- The cost difference between bimekizumab and comparators is most sensitive to assumptions about the rate of discontinuation from maintenance treatment and [redacted]. Results are insensitive to the probability that patients have a PASI reduction of at least 75% over the induction period, when the same probability is assumed for bimekizumab and comparators.

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

5.1 Strengths

- The ERG considers the phase III bimekizumab trials to be well designed and executed, with low risk of bias. The patient populations in the trials, overall, appear to be representative of patients typically seen in practice in the NHS.
- The company's indirect comparison of bimekizumab to its chosen cost comparators is based on standard NICE DSU methodology, with comprehensive scenario analyses to explore the use of different assumptions around proportional treatment effects and baseline risk. The ERG concurs with the company's assumptions and choice of modelling methods.
- The structure and key assumptions of the company's cost-comparison model are appropriate, and consistent with previous cost-comparisons (risankizumab TA596 and guselkumab TA521) and cost-effectiveness analyses for other comparators (ixekizumab TA442 and brodalumab TA511).
- Results of the company's NMA supports the assumption of similar efficacy for bimekizumab and comparators is required for the cost-comparison.

5.2 Weaknesses and areas of uncertainty

- There is apparent heterogeneity in the NMA in terms of the proportion of patients in the trials who had previously received biologic therapy, a potential treatment effect modifier. However, the ERG does not consider that this biases in favour of bimekizumab.
- Based on list prices for all treatments, bimekizumab is more costly than the comparators risankizumab, ixekizumab and brodalumab. This applies to the company's base case analysis and for all company and ERG sensitivity and scenario analyses. Results based on PAS discounts for bimekizumab and comparators are shown in a confidential addendum to this report.
- The cost difference between bimekizumab and comparators is most sensitive to assumptions about the rate of discontinuation from maintenance treatment and [redacted].

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