NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

FAST TRACK APPRAISAL (FTA)

Guselkumab for treating moderate to severe plaque psoriasis [ID1075]

The following documents are made available to the consultees and commentators:

1. **Technical Briefing**

   Final Scope and Final Matrix see -
   https://www.nice.org.uk/guidance/indevelopment/gid-ta10232/documents

2. **Company cost comparison summary** from Janssen

3. **Clarification letters**
   - **NICE request** to the company for clarification on their submission
   - **Company response** to NICE's request for clarification
     - **Additional response** to questions A5 and A9
     - **Further additional** response to question A9

4. **Patient group, professional group and NHS organisation submission** from:
   - **Psoriasis and Psoriatic Arthritis Alliance**
   - **British Association of Dermatologists**
   - **British Society for Rheumatology**

   The Royal College of Physicians endorses British Society for Rheumatology submission

5. **Expert personal perspectives** from:
   - **Clinical expert**, nominated by British Dermatology Nursing Group
     - **Response to additional questions** from **clinical expert**
   - **Clinical expert**, nominated by Janssen

   Please note that Clinical expert nominated by British Association of Dermatologists (BAD) endorsed their submission and did not submit an expert statement

6. **Evidence Review Group full report** prepared by Warwick Evidence Group

7. **Company additional analyses**
    - **ERG addendum: ERG comments on the company's additional analyses**

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

9. **Evidence Review Group report – erratum**

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

Technical briefing

Guselkumab for treating moderate to severe plaque psoriasis

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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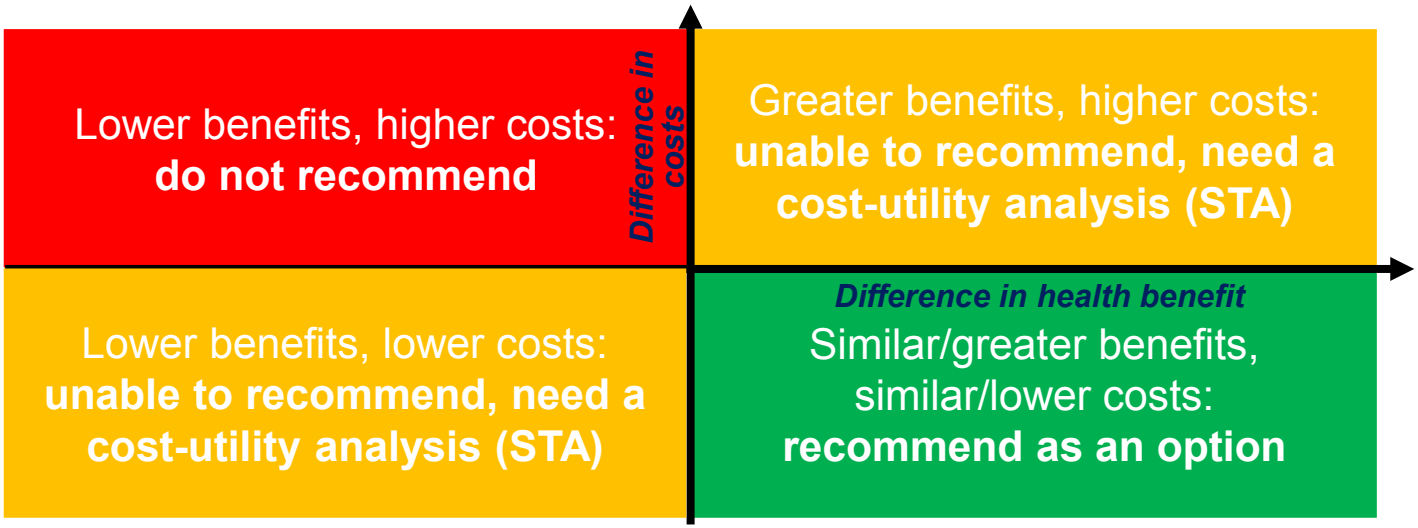
Fast Track Appraisals: Cost comparison

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:



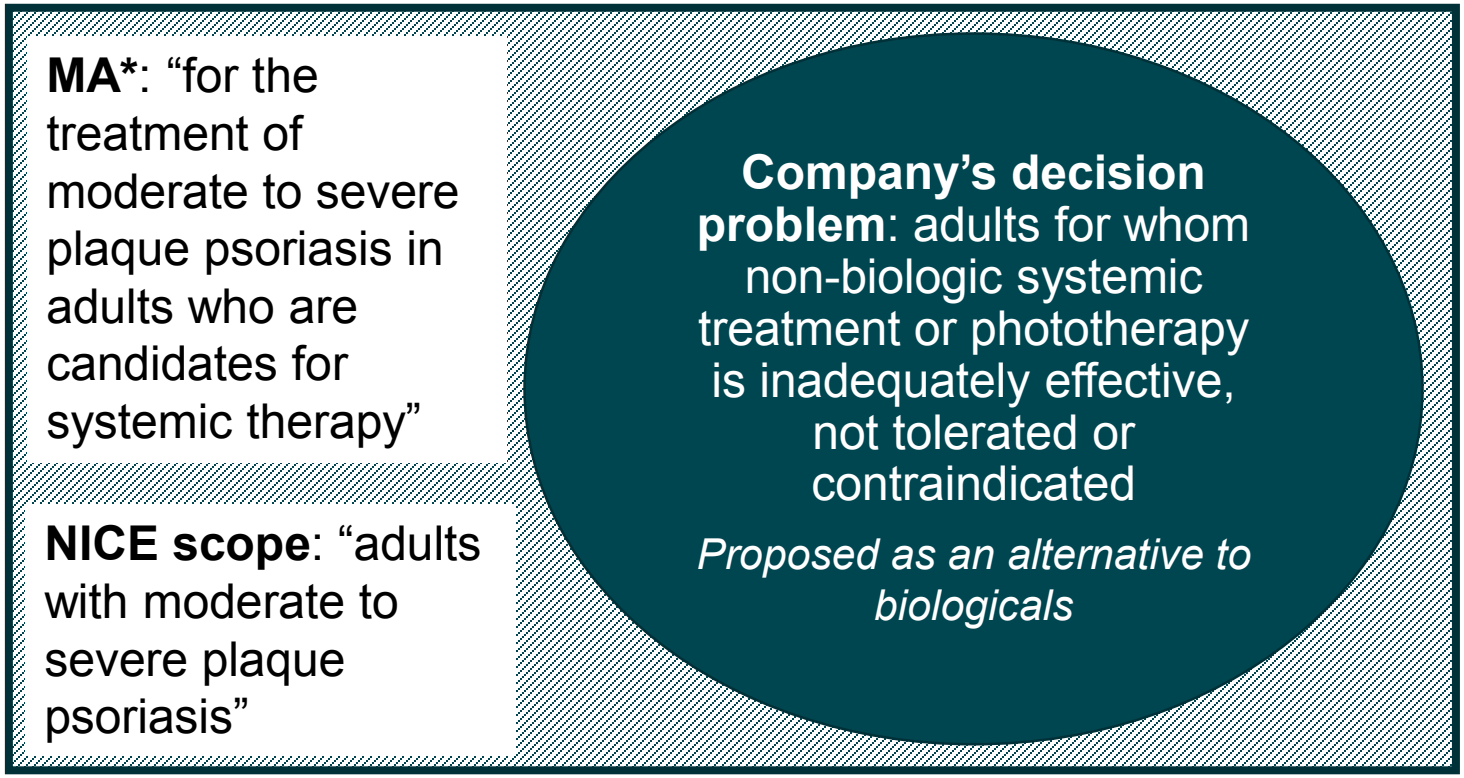
  - If a technology is recommended through cost comparison, guidance states:
    - *"If patients and their clinicians consider both <the technology and comparators> to be suitable treatments, the least costly should be used"*

Key issues

- ***This topic is proposed as an FTA using cost comparison methods***
  - Considered if the technology provides **similar/greater benefits** at **similar/lower cost** vs a **NICE-recommended** comparator
- Does the committee agree that the clinical evidence shows that guselkumab provides similar or greater benefits vs the comparators?
  - Head-to-head: vs adalimumab
  - NMA: vs TNF-alpha inhibitors, ustekinumab, secukinumab, ixekizumab
- Which cost analysis is most relevant for decision-making?
  - Simple annual price comparison
  - Company analysis (assuming similar effectiveness) vs adalimumab and ustekinumab
  - ERG exploratory analysis (using NMA effectiveness estimates)
    - vs adalimumab and ustekinumab
    - vs other comparators (including ixekizumab)

Decision problem – population

Company focuses on narrower population than NICE scope and marketing authorisation, which reflects likely position of guselkumab in NHS clinical practice



- **ERG comment**: Company's decision problem is relevant to clinical practice
- Previous appraisals of biologicals for psoriasis included broad patient populations, but recommendations were restricted based on the expected use of biologicals in the treatment pathway

***MA**: marketing authorisation

1st

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

2nd

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

3rd

Systemic non-biological therapy
methotrexate, ciclosporin, acitretin

4th

Systemic biological therapy

Severe (PASI ≥10 & DLQI >10)
adalimumab (TA146)
etanercept (TA103)
ixekizumab (TA442)
secukinumab (TA350)
ustekinumab (TA180)

Very severe
(PASI ≥20 & DLQI >18)
infliximab (TA134)

May be used in sequence

Guselkumab for moderate to severe psoriasis?

Proposed as an alternative to systemic biologicals

Severe (PASI ≥10 & DLQI >10)
apremilast (TA419)
dimethyl fumarate (TA475)

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

BSC

Best supportive care

Company's positioning of guselkumab

Intervention and comparators

	Intervention: Guselkumab	Comparators: Systemic biological therapies
Mechanism of action	Interleukin (IL)-23 inhibitor	TNF-alfa inhibitors (etanercept[1], infliximab[2], adalimumab[3]) IL12/23 inhibitor (ustekinumab[4]) IL-17 inhibitors (secukinumab[5], ixekizumab[6])
Indication	*MA:* "moderate to severe plaque psoriasis in adults who are candidates for systemic therapy" *Company proposal:* patients for whom systemic biologic therapy is suitable	*MA:* moderate to severe plaque psoriasis, if: • other systemic therapies unsuitable (1,2,4) • candidate for systemic therapy (3,4,6) *NICE recommendation:* • severe disease* that has not responded to standard systemic therapies • stop if insufficient response at 12–16 wks
Admin schedule	Induction: injections at wks 0 and 4 Maintenance: every 8 wks	*Depending on drug:* Induction: injection schedule over 12–16 wks Maintenance: every 1–12 wks

*PASI ≥10, DLQI ≥10

Market share – subcutaneous biologicals 2014–2017

- Adalimumab has a [redacted] market share
- Ustekinumab has a [redacted]
- While, secukinumab has a [redacted]

Comparators: NICE technology appraisals

Guidance	TA103: etanercept TA134: infliximab	TA146: adalimumab TA180: ustekinumab	TA350: secukinumab TA442: ixekizumab
Clinical effectiveness	• Key outcomes: PASI response rates (notably PASI75[§]), DLQI • TA442: PASI75 rates for comparators were 41–82%[+] • Ixekizumab was more effective than adalimumab and ustekinumab and similar to infliximab and secukinumab		

Economic modelling	• State transition models based on PASI response rates
	  • Patients with PASI75 response after induction continue to maintenance
	  • Utilities based on PASI responses
	  • Long-term discontinuation during maintenance at fixed rate: 20% per year generally accepted by committee
	• More recently, consideration given to sequences of biologicals – sequencing analyses were uncertain and decisions primarily based on comparison of pairwise ICERs		

Cost effectiveness	• Most plausible ICERs have not been precisely defined • TA180: “no robust difference in cost effectiveness between ustekinumab and adalimumab” • TA350 and TA442: ICERs likely to be in line with other recommendations		

[§]PASI 75: proportion achieving ≥75% improvement in baseline PASI score [+]Etanercept and secukinumab respectively; results for ixekizumab were confidential

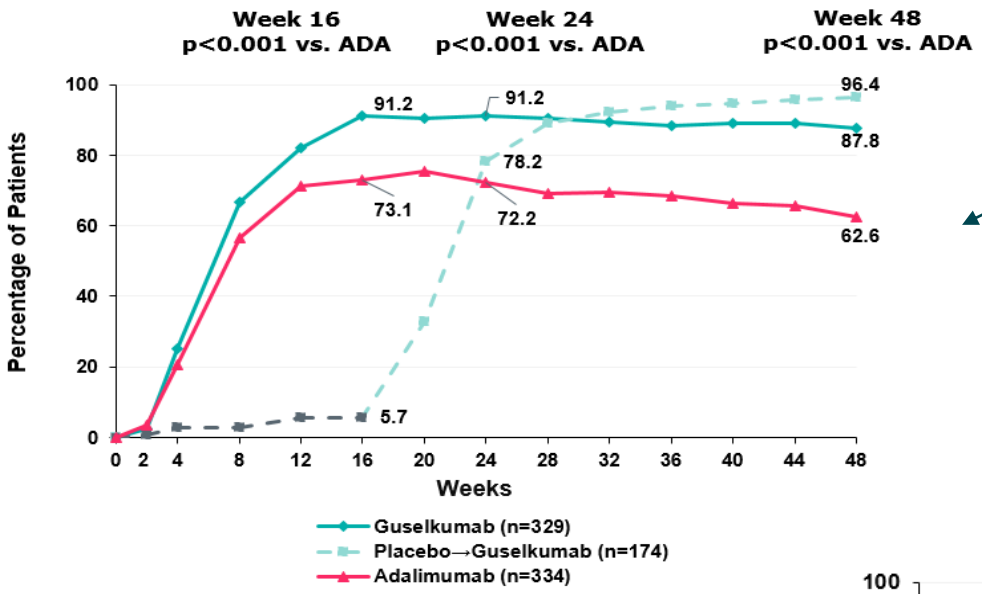
Clinical effectiveness evidence

- **3 Phase III randomised controlled trials**
  - VOYAGE-1 } *placebo and active controlled (adalimumab) trials +*
  - VOYAGE-2 } *open-label extension*
  - NAVIGATE } *trial of switching to guselkumab vs ustekinumab after inadequate response to ustekinumab*
- **Primary outcomes**: PASI 90 at Week 16, IGA 0/1 at Week 16
- **Secondary outcomes**: DLQI at Week 16, IGA 0/1 at Week 16, 24, 48, 28-40; PASI 75 at week 16; PASI 90 at Week 16, 24, 48
- **Definition of trial population**: 'adults with psoriasis, who had not previously received guselkumab or adalimumab/ustekinumab'

	VOYAGE-1	VOYAGE-2	NAVIGATE
	n=836	n=992	n=268
Mean age (yrs)	44	43	44
Sex (% men)	72%	70%	68%
Mean duration of psoriasis (yrs)	18 yrs	18 yrs	17 yrs
Prior biological treatment	21%	21%	22%

PASI75 results of VOYAGE 1, VOYAGE 2

Guselkumab is more effective than adalimumab measured by PASI 75 at Week 16 and Week 24

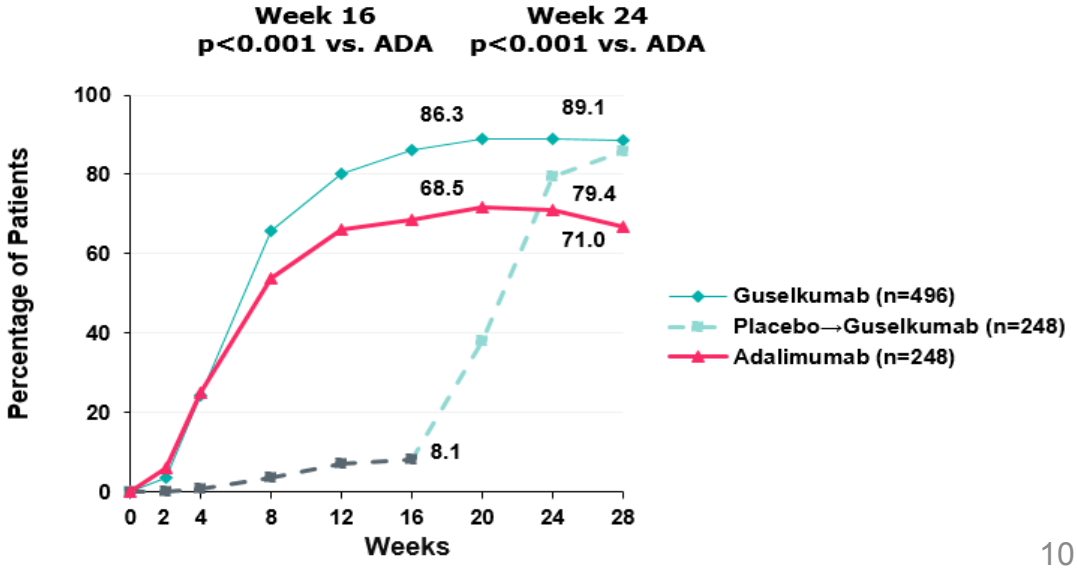


Voyage 1

PASI75 at week 16: 91.2% guselkumab vs. 73.1% adalimumab

Voyage 2

PASI75 at week 16: 86.3% guselkumab vs. 68.5% adalimumab



Source: Figure 6 and Figure 10 of company submission

Network meta-analysis

- Network meta-analyses (NMAs) involving 45 randomised controlled trials
  - Guselkumab vs all possible systemic biological psoriasis treatments
- 2 sets of analyses:
  - Full NMA: comprised all possible biologicals, including agents and doses unlicensed in the UK
  - Restricted NMA: comprised only comparators specified in the decision problem
- Random effect model
- Adjusted for placebo response rate (termed *'baseline risk-adjusted analysis'; unadjusted analyses and analyses adjusted for duration of psoriasis also performed but not presented here*)
- Outcomes:
  - efficacy (PASI 90, PASI 75, PASI 50, PASI 100, PGA/IGA)
  - safety (adverse event, serious adverse event , withdrawal due to adverse event)
  - HRQL (DLQI)
- Relative effects reported as risk ratios (RR) and associated 95% credible intervals (CrI)
- **ERG comment:** considered the 'restricted NMA' to be more appropriate than the 'full NMA' and consistent with the final scope

NMA results – Pairwise comparison, baseline risk-adjusted

Guselkumab is more effective than other systemic biological agents except ixekizumab

Guselkumab has similar safety profile compared with other biologicals

	PASI 75 response (%)	Risk Ratio* (*95% CrI*) Guselkumab vs. comparators
Guselkumab	[redacted]	
Adalimumab	[redacted]	1.24 *(1.18–1.32)*
Ustekinumab 45mg	[redacted]	1.27 *(1.18–1.37)*
Etanercept QW	[redacted]	2.40 *(1.95–2.98)*
Secukinumab	[redacted]	1.07 *(1.01–1.13)*
Ixekizumab	[redacted]	**0.98** *(0.93–1.02)*
		* Values >1 favour guselkumab

- Efficacy NMAs show that guselkumab is more effective than anti-TNF, ustekinumab and secukinumab, and similar to ixekizumab
- Safety NMAs show that guselkumab has a similar safety profile to other biologicals, regardless of treatment class

ERG review
Clinical effectiveness evidence

- Trials of guselkumab included a proportion of people (21%) who had previously received biological treatment → overall the trials adequately reflected the NHS population and the expected use of guselkumab
  - Findings from VOYAGE reflect favourably on guselkumab because of choice of comparator (adalimumab previously found to be less effective than anti-IL drugs)
- NMA: ERG considered the analysis to be good quality, and the results were broadly consistent with previous NICE technology appraisals
  - Some queries were raised, but their impact on the results was expected to be minimal
- Longer term real-world data on effectiveness and safety is lacking for the newer anti-IL agents (guselkumab, ixekizumab, secukinumab)

Additional considerations
Expert submissions

Clinical experts

- ‘Guselkumab is highly effective drug as shown by the clinical trial program. It is statistically superior to adalimumab and also works in patients better than ustekinumab’
- ‘Given it is highly effective in clinical trials AND has the inherent advantage of infrequent dosing versus IL-17s and adalimumab it is likely, that once is safety is established in the real world, it will be used early in the biologicals treatment pathway’
- ‘Adverse events are very low’
- ‘It is likely that guselkumab, being dosed every 8 weeks, will also show the same beneficial persistence [as ustekinumab] in the medium- to long-term’
- ‘This is why in my opinion guselkumab with its dosing advantage becomes an important drug for the coming years’

Comparison of 1st year and maintenance annual costs

[redacted]

	Induction	1st year
Guselkumab	[redacted]	[redacted]
Ixekizumab	£7,880	£19,130
Secukinumab	£7,310	£18,280
Ustekinumab	£4,290	£10,740
Adalimumab	£3,520	£9,680
Etanercept biosimilar	£1,970	£8,530
Etanercept	£2,150	£9,300

Annual thereafter	
Guselkumab	[redacted]
Ixekizumab	£14,630
Secukinumab	£14,630
Ustekinumab	£9,300
Adalimumab	£9,160
Etanercept biosimilar	£8,530
Etanercept	£9,300

Figures are rounded

Ixekizumab and secukinumab have confidential comparator PASs - see accompanying appendix

Cost comparison analysis

- Company presented a cost comparison analysis comparing guselkumab with adalimumab and ustekinumab
  - Adalimumab and ustekinumab are [redacted] biologicals with [redacted] and [redacted] of the market respectively
- Assumed that people stop treatment if their disease does not respond sufficiently (PASI75) at week 12–16 (per NICE stopping rules)
- Assuming similar efficacy across treatments: [redacted] of patients have PASI75 response and continue therapy after induction
- Long-term discontinuation rate: 20% for all treatments (consistent with previous STAs)
- 5-year time horizon

- *Company also presented a sequencing analysis, modelling costs for 3 sequences of biologicals*
  - *ERG highlighted significant limitations in the analysis*
  - *Full analysis of treatment sequences is not feasible within FTA cost comparison*

Company's cost comparison analysis

	Total cost	Difference vs guselkumab
Guselkumab	[redacted]	
Adalimumab	**£25,790**	[redacted]
Ustekinumab	**£27,930**	[redacted]

Figures are rounded

- Total costs of treatment
  - Over 5 years
  - Taking into account discontinuation after induction treatment failure (assuming similar effectiveness)
  - and long-term discontinuation

[redacted]

ERG's review
Cost comparison analysis

- ERG commented that assuming similar efficacy (PASI75 response) is inappropriate
  - Statistically significant differences between treatments
  - Influences treatment duration and hence cost to NHS
- ERG therefore presented an exploratory analysis:
  - Based on PASI75 results from NMA
  - Including [redacted] of biologicals
  - Including all sub-cut biologicals as comparators
  - Corrected errors in company modelling
  - Time horizon: 10 years (5 years explored in scenario analysis, not shown)
  - ERG also explored different long-term discontinuation rates in a scenario analysis (not shown)

ERG exploratory analysis

Cost comparison with biologicals

	Assuming similar efficacy	Efficacy based on NMA
	10 year	*10 year*
Etanercept	£38,160	£17,340
Adalimumab	£39,010	£32,120
Ustekinumab	£41,100	£33,430
Secukinumab	£61,230	£57,730
Ixekizumab	£61,990	£63,090
Guselkumab	[redacted]	[redacted]

Ixekizumab and secukinumab have confidential comparator PASs - see accompanying appendix

Figures are rounded

- Total costs of treatment
  - Over 10 years, taking into account discontinuation after induction treatment failure (assuming similar effectiveness/using efficacy estimates based on NMA results) and long-term discontinuation

ERG exploratory analysis, 10 year costs

[redacted]

[redacted]

Difference (%) vs guselkumab

£61,990
£61,230
£41,100
£39,010
£38,160

Ixekizumab and secukinumab have confidential comparator PASs - see accompanying appendix

[redacted]

Difference (%) vs guselkumab

£63,090
£57,730
£33,430
£32,120
£17,340

ERG review: additional comments

- Company analysis focuses on adalimumab and ustekinumab – although [redacted] so may be less relevant
  - Applying the central NMA estimates → guselkumab is more effective and [redacted] than adalimumab and ustekinumab
- Scenario analysis includes remaining comparators
  - Secukinumab has a [redacted] – may be displaced by guselkumab
  - Ixekizumab appears to be the most effective biological, and guselkumab is similarly effective
    - Although [redacted], may be expected to increase – *supported by clinical expert submissions*
    - In a full model, QALY gain would be expected to be similar for guselkumab vs ixekizumab – decision would likely come down to comparison of costs

Technical team view and rationale

Decision problem: Adequate and potentially suitable for cost comparison FTA

- Proposed population is narrower than the scope but consistent with previous appraisals
- Compared with relevant NICE-recommended comparators

Clinical evidence: Likely to provide similar or greater benefits vs comparators

- Head-to-head trial shows significant superiority over adalimumab
- NMA shows greater effectiveness than most biologicals, and similar to ixekizumab

Economic evidence: Simple comparison of annual costs or ERG cost comparison with ixekizumab may be sufficient for decision-making

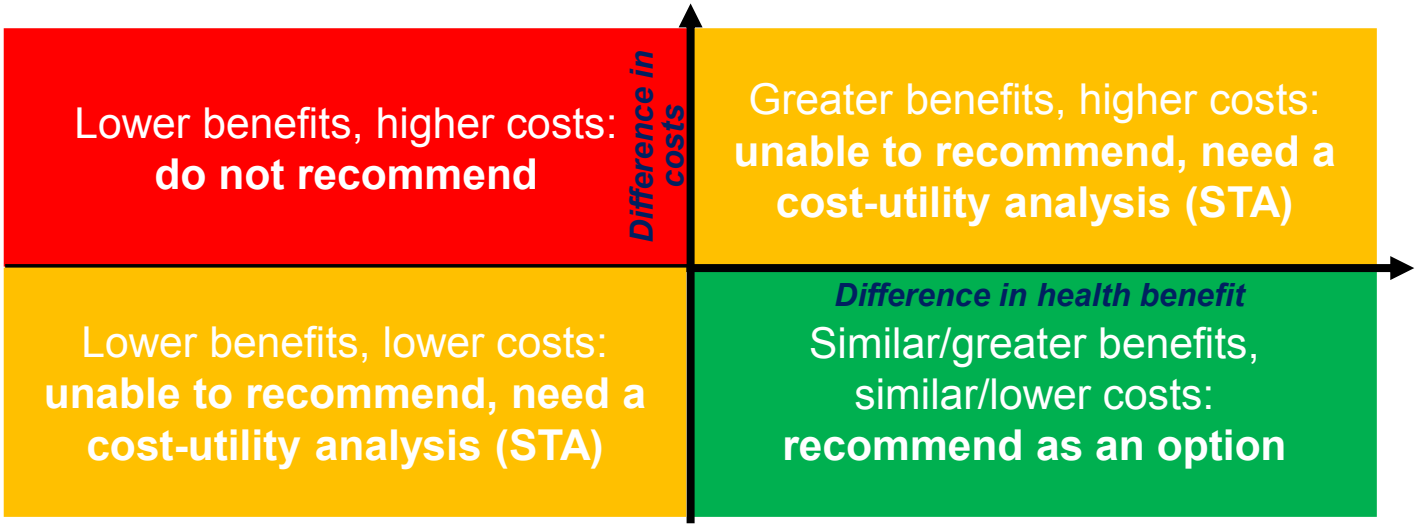
- Simple comparison of annual costs may be sufficient for decision-making
- Company cost comparison (assuming similar efficacy) shows guselkumab is [redacted] than adalimumab and [redacted] than ustekinumab
- ERG highlights that greater effectiveness would influence cost
  - In this case, guselkumab appears more effective and [redacted] than adalimumab and ustekinumab *([redacted])*
  - However, comparison with ixekizumab (to which guselkumab is similar in effectiveness) may be relevant *(see confidential appendix)*

Key issues and possible recommendations (1)

- **This topic is proposed as an FTA using cost comparison methods**
  - Considered if the technology provides **similar/greater benefits** at **similar/lower** cost vs a **NICE-recommended** comparator
- Does the committee agree that the clinical evidence shows that guselkumab provides similar or greater benefits vs the comparators?
  - Head-to-head: vs adalimumab
  - NMA: vs TNF-alpha inhibitors, ustekinumab, secukinumab, ixekizumab
- Which cost analysis is most relevant for decision-making?
  - Simple annual price comparison
  - Company analysis (assuming similar effectiveness) vs adalimumab and ustekinumab
    - guselkumab is [redacted] than adalimumab and [redacted] than ustekinumab
  - ERG exploratory analysis (using NMA effectiveness estimates)
    - vs adalimumab and ustekinumab - guselkumab is [redacted] and more effective
    - vs other comparators (including ixekizumab) - similarly effective, costs based on comparator PASs (see accompanying appendix)

Key issues and possible recommendations (2)

- In light of the above, should guselkumab be recommended?
  - Consistently with previous NICE recommendations
    - *Severe disease that has not responded to standard systemic therapies, stop if insufficient response at 12–16 wks)*
  - Including standard FTA statement
    - "*If patients and their clinicians consider both <the technology and comparators> to be suitable treatments, the least costly should be used*"



Confidential Appendix

There are confidential patient access schemes for guselkumab, secukinumab and ixekizumab; therefore, results of the cost comparison taking these discounts into account are presented in a confidential appendix.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

Guselkumab for treating moderate to severe plaque psoriasis [ID1075]

Document B

Company evidence submission

October 2017

File name	Version	Contains confidential information	Date
ID1075_Guselkumab NICE FTA Document B_Final		**Yes**	**25.10.17**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) when a cost-comparison case is made as part of the fast track technology appraisal process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the fast track appraisal user guide.

This submission must not be longer than 100 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

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

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

Highlighting in the template (excluding the contents list)

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

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

Contents

Tables and figures

Executive summary

Guselkumab (Tremfya®) is a novel human monoclonal antibody that targets interleukin-23 (IL-23) which has been shown to play a key role in the immune-mediated inflammatory disease pathway in psoriasis.

Psoriasis is a painful, relapsing and remitting chronic dermatologic condition characterised by autoimmune-mediated inflammation of the skin. The prevalence of adult psoriasis in England and Wales is estimated to be 1.75%[1] which is approximately 838,000 people; plaque psoriasis accounts for up to 90%[2] of the cases of whom it is estimated 20% have moderate to severe psoriasis (15% moderate, 5% severe), [3] equating to 150,000 people. It has been estimated, however, that only 2.55%[4] of the population with plaque psoriasis are actually treated with biologics, equivalent to 21,000 patients.

Onset of psoriasis typically occurs between the ages of 20 to 40[5], affecting younger and working age people in their most formative and productive years. Physical symptoms go beyond skin manifestations and include significant pain and discomfort that affect mood, ability to perform daily activities or even to hold gainful employment. Unsightly plaques impact a patient's ability to approach relationships with confidence leading to self-imposed isolation. Anxiety, depression and suicidal ideation are frequent comorbidities and the quality of life of patients living with severe psoriasis is generally poor.

Skin inflammation associated with psoriasis is mediated by multiple cytokines, including tumour necrosis factor alpha (TNF-α) and several interleukins, including IL-12, IL-17 and IL-23. The goal of disease modifying therapies in psoriasis is to achieve long-term remission leading to an improved quality of life. The involvement of multiple cytokines poses a challenge in achieving this long-term remission as patients stop responding to a therapy over time. Consequently, availability of various biological interventions is highly desirable in psoriasis. Current treatment options include anti-TNF and other cytokine modulators. Adalimumab and ustekinumab are the most widely prescribed biologics with [redacted] and [redacted] of the market respectively, which accumulate over two thirds of the total biologics market.

Guselkumab offers a novel mode of action with a targeted inhibition of IL-23, which provides an effective blockade of the interleukin 23 inflammatory pathway involved in psoriatic lesion formation. Three Phase III randomised active controlled trials (RCT), VOYAGE 1, VOYAGE 2, and NAVIGATE evaluated and demonstrated efficacy and safety of guselkumab as a treatment for moderate to severe plaque psoriasis. A wide range of outcome were measured, including co-primary endpoints Investigator's Global Assessment (IGA) and Psoriasis Area Severity Index (PASI) 90, and various secondary endpoints including PASI 100, PASI 75, PASI 50, localised psoriasis measurements and quality of life such as Dermatology Life Quality Index (DLQI) and Psoriasis Symptoms and Signs Diary (PSSD).

In the trials, guselkumab in comparison to adalimumab delivered superior, sustained and symptom free skin clearance leading to normalised health related quality of life. Guselkumab also demonstrated a significant reduction in comorbidities such as anxiety, depression and improved overall work productivity.

Based on the RCT results, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on 14 September 2017 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. The European Commission (EC) is expected to grant a marketing authorisation in November 2017.

In addition to the clinical trial results with head-to-head superiority to adalimumab, a network meta-analysis (NMA) was performed to assess the relative efficacy of guselkumab versus other biologic therapies recommended by NICE. The efficacy NMA showed that guselkumab is superior to anti-TNF (including adalimumab), IL 12/23 ustekinumab and IL-17 secukinumab, and non-inferior to IL-17 ixekizumab. The safety NMA indicated that guselkumab has a similar safety profile to other biologics. It should also be noted that guselkumab provides these comparable (or superior) health benefits and safety through a reduced dosing schedule, conducted in the comfort of the patients own home.

Guselkumab will be made available at a list price of £2,250.00 per prefilled syringe. [redacted]

On the basis of guselkumab's efficacy results, safety profile and annual treatment costs compared to biological therapies, Janssen proposed to NICE that this appraisal should be based on the fast track appraisal (FTA) process. This submission is restricted to patients with moderate to severe plaque psoriasis that have failed conventional systemic therapies and therefore excludes patients that are candidates for these therapies.

A cost-comparison was carried out against the current market leaders in terms of number of patients treated per year: adalimumab and ustekinumab. Our analysis confirms that guselkumab is cost-effective [redacted]

In conclusion, guselkumab presents a cost-effective option with a novel mode of action that is likely to help patients with moderate to severe psoriasis achieve high levels of sustained symptom-free skin clearance with minimal budget impact, representing value for money for the NHS.

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

B.1.1. Decision problem

Guselkumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. This submission focuses on patients with moderate to severe disease for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. The proposed positioning is narrower than the marketing authorisation to align with NHS clinical practice; guselkumab would be used in patients in line with the position of existing biologic therapies in the psoriasis pathway of care, that is, after conventional systemic therapy. In previous technology appraisals[6-11], NICE have recommended biological therapies as a treatment option for adults with plaque psoriasis when the following criteria are met:

- The disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
- The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant of, or has a contraindication to, these treatments.

Of note, while the final scope also included apremilast and dimethyl fumarate (DMF) as potential comparators for patients with severe (or very severe) psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated (in line with their licence terms and NICE recommendations), NICE heard from clinical experts how such therapies would not displace biologic therapies during their recent appraisals.[12, 13] Apremilast and DMF are small molecule, non-biologic, oral treatments with significantly lower degrees of efficacy and differing safety profiles to the biologic therapies and would only be considered for use in patients unsuitable for biologic treatment or unwilling to receive biologic treatment. [12-15] Guselkumab would not displace apremilast or DMF, only the

existing biological therapies. Considering this, at the Decision Problem Meeting, the NICE technical team verbally advised that the cost-comparison case be made only against alternative biologic treatment. This is in line with general NICE guidance that the clinical and economic case be made against the relevant comparators for the proposed positioning; that is against alternative biological therapy in the case of guselkumab.

The decision problem that the submission addresses is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate to severe plaque psoriasis	Adults with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated	This aligns the target population for guselkumab to patients for whom systemic biologic therapy is considered suitable, and thus the population currently receiving biologic treatment(s) in clinical practice
Intervention	Guselkumab	Guselkumab	Not applicable
Comparators	If non-biologic systemic treatment or phototherapy is suitable: • Systemic non-biological therapies including acitretin, ciclosporin, fumaric acid esters (including dimethyl fumarate; subject to ongoing NICE appraisal) and methotrexate • Phototherapy with ultraviolet (UVB) radiation For people with severe or very severe psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated: • TNF-alpha inhibitors (etanercept, infliximab, adalimumab) • Ustekinumab • Secukinumab	• TNF-alpha inhibitors (etanercept, infliximab, adalimumab) • Ustekinumab • Secukinumab • Ixekizumab	The target population for guselkumab submission is patients for whom systemic biologic treatment is considered suitable. While the final scope also included apremilast and dimethyl fumarate (DMF) as potential comparators (in line with their licence terms and NICE recommendations), NICE TAGs stated that such therapies would not displace biological therapies during their recent appraisals.[12, 13] Therefore, guselkumab would not displace apremilast or DMF, only the existing biologic treatments. Considering this, at the Decision Problem meeting, the NICE technical team verbally advised that the cost-comparison case should only be made against alternative biologic treatments. This is in line with general NICE guidance that the clinical and

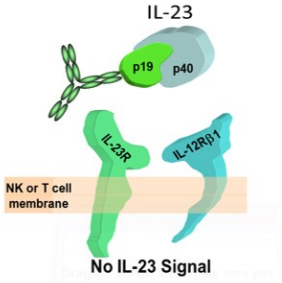
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Apremilast • Ixekizumab • Dimethyl fumarate (subject to ongoing NICE appraisal) • Best supportive care		economic case be made against the relevant comparators for the proposed positioning, that is, against alternative biological therapy in the case of guselkumab.
Outcomes	The outcome measures to be considered include: • Severity of psoriasis • Psoriasis symptoms on the face, scalp and nails • Response and remission rate • Relapse rate • Mortality • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Severity of psoriasis • Psoriasis symptoms on the face, scalp and nails • Response and remission rate (as represented by skin clearance) • Relapse rate (as represented by loss of response) • Mortality • Adverse effects of treatment • Health-related quality of life	Not applicable
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	A cost comparison versus ustekinumab has been carried out. The time horizon for assessing cost is 5 years, which is sufficiently long to capture the majority of costs associated with the use of guselkumab consistent with the 20% discontinuation rate used in previous appraisals.	We believe that guselkumab can be appropriately assessed through the Fast Track Appraisal process, due to its similarity in terms of costs and effectiveness with currently approved comparator therapies. As such, we have submitted a cost comparison analysis. The cost comparison compares the drug acquisition costs for guselkumab versus adalimumab

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. For the comparators, the availability and cost of biosimilars should be taken into consideration.	Costs are considered from an NHS and Personal Social Services perspective. A patient access scheme for guselkumab has been included as part of the analysis.	and ustekinumab. Only one therapy is required for comparison for a Fast Track Appraisal. Adalimumab and ustekinumab were selected as the most appropriate comparators given their wide usage in clinical practice, and its comparability to the remaining comparators in terms of cost and effectiveness (Section B.4.2).
Key: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; TNF, tumour necrosis factor; UVB, ultraviolet B.			

B.1.2. Description of the technology being appraised

Details of the technology being appraised in this submission are summarised in Table 2. The summary of product characteristics (SmPC) and draft European public assessment report is provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Guselkumab (Tremfya®)
Mechanism of action	Guselkumab is a human immunoglobulin 1 lambda (IgG1λ) mAb that binds selectively to the p19 protein subunit of IL-23 protein with high specificity and affinity, as depicted below. IL-23 is a regulatory cytokine that affects the differentiation, expansion, and survival of T cell subsets, (e.g., T helper 17 [Th17] cells and IL-17-secreting CD8 T [Tc17] cells) and innate immune cell subsets, which represent sources of effector cytokines, including IL-17A, IL-17F and IL-22 that drive inflammatory disease. Levels of IL-23 are elevated in the skin of patients with plaque psoriasis. Through high specificity and binding to p19, as depicted below, guselkumab blocks interaction of IL-23 and its cell-surface receptor, thereby disrupting IL-23-mediated signalling, activation, and cytokine cascades. Guselkumab may thereby provide a more targeted and upstream blockage of inflammatory pathways involved in psoriasis lesion formation than other therapies. 
Marketing authorisation	CHMP positive opinion was received on 14 September 2017, with anticipated marketing authorisation in November 2017.
Indication and any restriction(s) as described in the summary of product characteristics	The approved indication for guselkumab is *"for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy"*. Contraindications for use are: • Serious hypersensitivity to the active substance or its excipients • Clinically important active infections e.g. tuberculosis
Method of administration and dosage	The recommended dose of guselkumab is 100mg by SC injection at Weeks 0 and 4, followed by a maintenance dose every 8 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Patients may self-inject if a physician determines that this is appropriate.

	Janssen funds a homecare service, through which the SC injection is administered to patients at home, either by self-injection following nurse training visits over the course of the first 2–3 doses, or by an ongoing nurse administration service for patients who are not suitable for self-injection.
Additional tests or investigations	No additional tests or investigations are needed. In accordance with routine clinical practice for the use of biologics, patients should be evaluated for tuberculosis infection prior to initiation of therapy.[16]
List price and average cost of a course of treatment	List price: £2,250 per 100mg dose Cost of treatment over a 5-year time horizon: £42,640
Patient access scheme	PAS price: [redacted] Annual treatment cost in year 1: [redacted] Average annual treatment cost in maintenance: [redacted]
Key: CHMP, Committee for Medicinal Products for Human Use; IL-23, interleukin 23; mAb, monoclonal antibody; PAS, patient access scheme; SC, subcutaneous.	

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

Disease overview

Psoriasis is a painful, disfiguring, and chronic dermatological condition characterised by autoimmune-mediated inflammation of the skin.[17, 18] Plaque psoriasis typically presents as lesions of itchy, dry, scaly and thickened skin, which can be physically and psychologically debilitating (particularly when located on the hands, feet, face, joints and genitals).[12, 19-23] Within a recent technology appraisal, TA 419[12], NICE heard how the visible nature of plaque psoriasis can make people feel isolated and lonely, which can lead to them losing self-confidence and avoiding social situations as well as affecting their career opportunities and influencing intimate relationships.[12]

Psoriasis patients often suffer from depression and anxiety[24, 25] with approximately 68% of sufferers reporting suicidal thoughts related to the issues with their skin.[26] Clinical experts in the UK estimate people with severe plaque psoriasis are approximately six times more likely to have suicidal thoughts or commit suicide than the general population.[12] Further serious comorbidities associated with psoriasis include cardiovascular (CV) disease[27, 28], metabolic syndrome[29, 30], diabetes[31] and chronic obstructive pulmonary disease.[32] Such comorbidities (particularly CV disease) contribute to an observed reduction in life expectancy for patients with

psoriasis[28, 33, 34], which is estimated at 3.5–4.4 years in patients with severe disease.[35]

Quantitative studies of health-related quality of life (HRQL) report that patients with psoriasis report significantly worse HRQL than the general population[36], a similar degree of HRQL impairment as patients with other serious chronic diseases (including cancer)[37], and a greater degree of HRQL impairment than patients with other serious dermatological conditions e.g. acne and eczema.[26] Not surprisingly, patients with severe psoriasis are more likely to report reduced HRQL than patients with moderate disease.[38] Following discussion of the impact of plaque psoriasis with patients and clinical experts, NICE recently concluded that severe plaque psoriasis has a significant psychosocial impact and substantially decreases quality of life.[12]

Onset of psoriasis may occur at any age, however, the majority of cases (~75%) occur before the age of 40[5], affecting patients at the prime of their working age and social life. The prevalence of psoriasis in the UK is estimated to be approximately 1.75%[1], with 80–90% of cases presenting as plaque psoriasis.[2] Approximately 20% of patients are estimated to have moderate to severe disease (15% moderate; 5% severe)[3], with 3% of psoriasis patients in England (equating to ~27,000 people) [39] estimated to be eligible for biologic treatment, representative of severe disease (Figure 1). Psoriatic nail disease and psoriatic arthritis (PsA) are estimated to affect 80–90% and up to 42% of plaque psoriasis patients, respectively.[40, 41]

Diagnosis and monitoring

Diagnosis and monitoring of plaque psoriasis is typically based on:

- The clinical appearance of skin lesions and skin symptom severity, assessed using one or more of the following measures: Psoriasis Area and Severity Index (PASI), percentage body surface area (BSA) or Investigators Global Assessment (IGA)/Physicians Global Assessment (PGA)
- The involvement of high-impact and difficult-to-treat sites, assessed using one or more of the following measures: Fingernail Physician's Global Assessment (f-PGA), Physician's Global Assessment of Hands and/or Feet (hf-PGA), Nail Psoriasis Area and Severity Index (NAPSI), Scalp-specific Investigator Global Assessment (ss-IGA)

- The impact of psoriasis on the physical, psychological and social wellbeing of the patient, assessed using one or more of the following measures: Dermatology Life Quality Index (DLQI), Medical Outcomes Study 36-Item Short Form (SF-36), Hospital Anxiety and Depression Scale (HADS), Work Limitations Questionnaire (WLQ)

These assessment measures are further detailed in Appendix D, along with the Psoriasis Symptom and Sign Diary (PSSD), which is an additional tool utilised in the guselkumab trials. This tool is designed to measure all major patient-reported symptoms and signs, and provide a comprehensive patient-reported outcome (PRO) tool for the assessment of treatment benefit.

Although there is no uniform definition of moderate to severe disease in clinical practice, severity is generally based on the BSA affected, the location of lesions, severity of skin symptoms, and response to treatment. Previous NICE technology appraisals have defined severe psoriasis as a total PASI of 10 or more and a DLQI of more than 10.[6, 8-11]

Clinical pathway of care

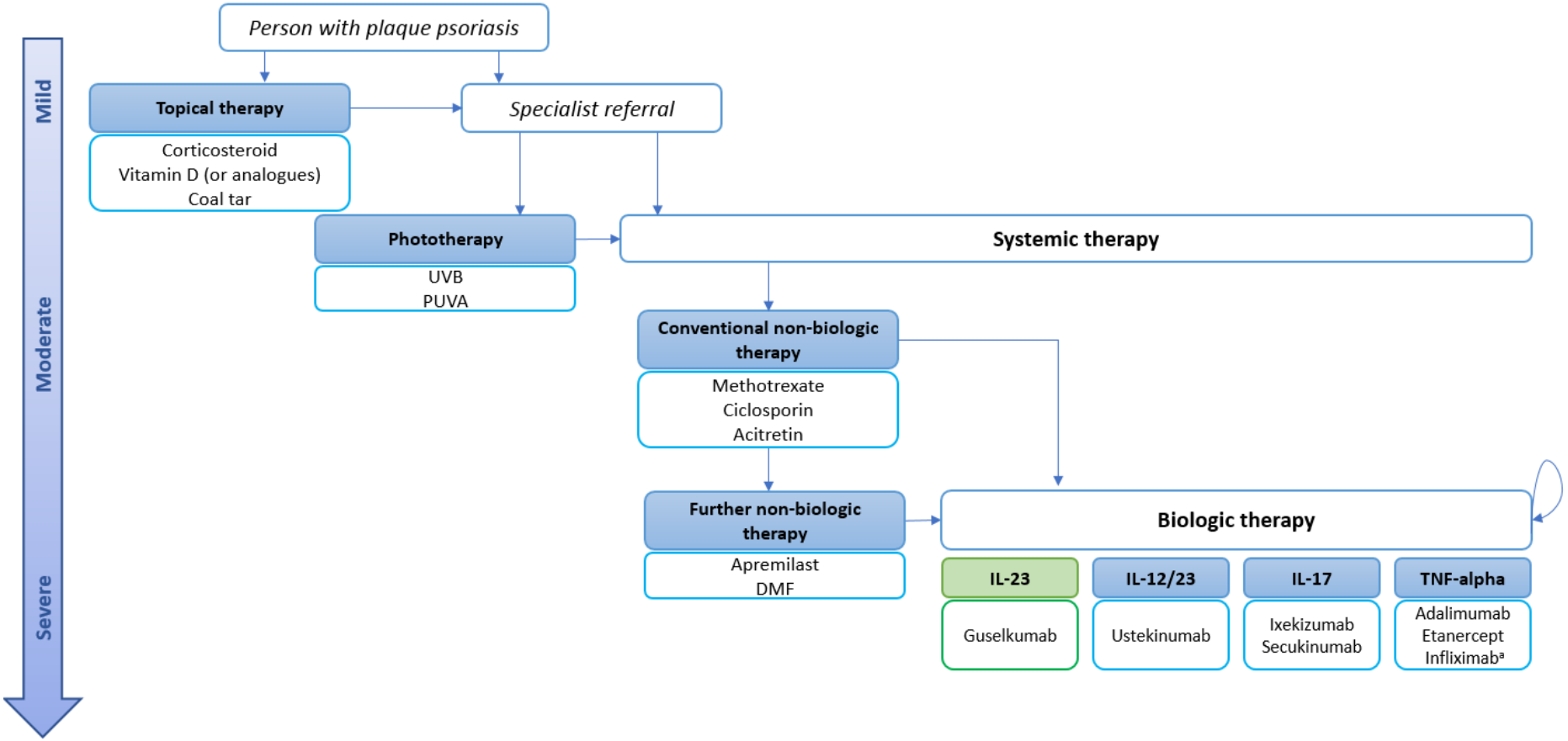
Treatment aims are to control signs and symptoms of disease, and to normalise patient quality of life. Measures by which these aims are assessed in clinical practice include the achievement of a PASI percentage improvement and an improvement in DLQI score. While a PASI 75 response is the traditional treatment aim, a PASI 90 response which is associated with a greater improvement in DLQI[42] is the modern, treatment goal in line with therapeutic advancements.[43-46]

The NICE pathway for psoriasis recommends topical therapies as first-line treatment, then optional phototherapy at second-line, followed by conventional systemic therapy (non-biologic treatments including methotrexate and ciclosporin) at third-line. If such therapies fail to adequately control the psoriasis, further treatment options for severe disease include apremilast, DMF or systemic biologic therapy. Patients considered suitable for systemic biological therapy (based upon both clinician and patient opinion) will be treated with the same biologic agent for as long as it continues to work. When their response to treatment starts to wane or they experience adverse side effects, patients will be offered a different biologic agent. This pattern is likely to

be repeated over their lifetime with psoriasis patients often trying multiple biological therapies in a short timeframe in current practice[12, 13]; presumably due to limitations of existing biologic agents, with loss of response over time commonly observed.[47-50]

Biologic agents currently available in the NHS include: the tumour necrosis factor-alpha (TNF-α) inhibitors, etanercept, infliximab, adalimumab; the interleukin(IL)-12/23 inhibitor, ustekinumab; and the IL-17 inhibitors, ixekizumab and secukinumab. Key features of these agents are summarised in Appendix D. The clinical pathway of care, and the proposed placement for guselkumab within this pathway (alongside existing biologic therapies) is summarised in Figure 1.

Figure 1: Clinical pathway of care and the proposed placement for guselkumab



Key: DMF, dimethyl fumarate; IL, interleukin; PUVA, psoralen plus ultraviolet light A; TNF, tumour necrosis factor; UVB, ultraviolet light B.
Notes: [a], Recommended for the treatment of very severe disease.
Source: Adapted from the NICE pathway for psoriasis and NICE Clinical Guideline CG153 (2012 updated 2017)[51, 52]

B.1.4. Equality considerations

No equality issues related to the use of guselkumab have been identified or are foreseen.

B.2. Key drivers of the cost-effectiveness of the comparator(s)

B.2.1. Clinical outcomes and measures

A total of six NICE technology appraisals have been published to date that relate to biologic treatment for moderate to severe plaque psoriasis. These are:

- TA103: Etanercept and efalizumab for the treatment of adults with psoriasis[6]
- TA134: Infliximab for the treatment of adults with psoriasis[7]
- TA146: Adalimumab for the treatment of adults with psoriasis[8]
- TA180: Ustekinumab for the treatment of adults with moderate to severe psoriasis[9]
- TA350: Secukinumab for treating moderate to severe plaque psoriasis[10]
- TA442: Ixekizumab for treating moderate to severe plaque psoriasis[11]

A further two appraisals have been published relating to non-biological systemic treatment for psoriasis:

- TA475: Dimethyl fumarate for treating moderate to severe plaque psoriasis[13]
- TA419: Apremilast for treating moderate to severe plaque psoriasis[12]

The focus of this section relates specifically to biologic treatments, as the relevant patient population is adults with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated.

Clinical effectiveness

The key clinical measure of effectiveness used within the economic modelling for previous NICE appraisals relating to biologic treatment was the PASI 75, that is, the

proportion of people achieving at least a 75% improvement in their baseline PASI score by assessment of response.

PASI 75 was identified within TA103 as a relevant measure of response based upon its use by the European Medicines Agency and the British Society for Rheumatology guidelines.[6] In the NICE appraisal of etanercept and efalizumab (TA103), however, the Committee agreed with expert testimony that a number of patients who do not achieve a PASI 75 would nevertheless derive significant benefit from treatment through improvements in quality of life. The Committee therefore considered that the assessment of response should also include a measure of quality of life improvement as defined by a change from the baseline DLQI at initiation of treatment. The Committee concluded that it would also be appropriate for individuals to continue treatment if they had achieved a PASI 50 response, providing they had also achieved a 5-point reduction in their DLQI score from when treatment was initiated. Biological therapies recommended for use by NICE after TA103 have included the DLQI basis for response alongside PASI 75, to ensure consistency between appraisals.

In addition to PASI 75 and PASI 50; PASI 90 and PASI 100 have also been considered by Committee B as indicators of clinical response to treatment, particularly in more recent appraisals; however, these measures of response have not been used as part of the recommendation criteria.[10, 11] We note that the aim of treatment for moderate to severe psoriasis is to control signs and symptoms of disease, and to normalise patient quality of life. Measures by which these aims are assessed in clinical practice include the achievement of a PASI percentage improvement, with a 75% improvement being the traditional treatment aim. However, a 90% improvement which is associated with a greater improvement in DLQI[42] should be the modern treatment goal in line with therapeutic advancements and clinical opinion.[43-46] We further note the positive results for guselkumab for this outcome (see Section B.3.9).

Table 3 summarises the respective Committee deliberations around PASI response.

Other clinical outcomes

In addition to discussions around definition of response, discontinuation and adverse event incidence have also been considered during Committee deliberations relating to clinical outcomes within the existing appraisals. Table 4 and Table 5 summarise the Committee deliberations around discontinuation and adverse event incidence, respectively.

With regards to discontinuation, an annual probability of 20% discontinuation for biologic treatment has been used consistently in every appraisal, and has generally been considered appropriate by each Committee (Table 4). For TA350 (secukinumab), the Committee noted that this discontinuation figure may be an overestimate when compared with clinical practice; however, the Committee noted that the overestimate would likely affect all biological therapies, and therefore concluded that this would have minimal impact on any estimate of cost-effectiveness.[10]

Adverse events have not been included within the considered NICE appraisals, (Table 5). Adverse event incidence was noted to be low, and similar across biological therapies.

Table 3: PASI response level considered in previous relevant appraisals

NICE TA	PASI response value used in cost-effectiveness modelling	Committee's preferred assumptions	Committee comments relating to PASI outcome
TA442 (ixekizumab)[11]	• PASI 75 • PASI 50 and PASI 90 used in scenario analyses	• PASI 75 or PASI 50 plus 5-point drop in DLQI, based upon recommendations in previous appraisals	• The Committee noted that PASI 75 was the primary outcome in the trial data used to model the cost-effectiveness of ixekizumab. • The Committee noted that, in previous appraisals, recommendations were made based on stopping treatment if there was an inadequate response; where an adequate response was defined as either a 75% reduction in the PASI score from when treatment started, or a 50% reduction in the PASI score and a 5-point reduction in DLQI from when treatment started. • The Committee therefore concluded that recommendations should be in line with previous appraisals for biological treatments in psoriasis.
TA350 (secukinumab)[10]	• PASI 75 • PASI 50 and PASI 90 in scenario analyses	• PASI 75 or PASI 50 plus 5-point drop in DLQI, based upon recommendations in previous appraisals • PASI 100 (complete clearance) was also considered a relevant secondary outcome	• The Committee considered that PASI and DLQI are relevant measures used in clinical practice in the NHS. • For PASI 75, the primary outcome in the trials, the Committee agreed that this demonstrated whether treatments for psoriasis had a high level of effectiveness. However, even with outcomes such as PASI 75, the psoriasis that remains could still have a significant impact on quality of life, and therefore, patients value any treatment that could completely clear the disease (that is, PASI 100). • The Committee concluded that PASI 75 was a clinically relevant definition of response to treatment and that, in addition, complete clearance was important; therefore, the evidence for PASI 100 should be taken into account when deciding the value of secukinumab to the NHS.

NICE TA	PASI response value used in cost-effectiveness modelling	Committee's preferred assumptions	Committee comments relating to PASI outcome
TA180 (ustekinumab)[9]	• PASI 75	• PASI 75 or PASI 50 plus 5-point drop in DLQI, based upon recommendation	• The Committee did not discuss the appropriateness or otherwise of various PASI response levels; however, the recommendation for ustekinumab related to an adequate response, defined as either a 75% reduction in the PASI score from when treatment started or a 50% reduction in the PASI score and a 5-point reduction in the DLQI score from when treatment started.
TA146 (adalimumab)[8]	• PASI 75 • PASI 50 in sensitivity analysis	• Response should be defined similarly to TA103, i.e. either PASI 75, or PASI 50 plus at least 5-point reduction in DLQI from baseline	• The Committee noted that the principal endpoint in the Phase III adalimumab trials was a PASI 75 response at 16 weeks. • The Committee concluded that it would be appropriate for treatment to be continued beyond 16 weeks only in people whose psoriasis had shown a PASI 75 response to treatment within 16 weeks. • In addition, the Committee agreed that the response criteria should be defined in a similar way to TA103 and should include an additional alternative criterion of a PASI 50 response and a 5-point reduction in the DLQI from start of treatment.
TA134 (infliximab)[7]	• PASI 75	• PASI 75 or PASI 50 plus 5-point drop in DLQI, based upon recommendations in previous appraisals	• The Committee noted that the principal endpoint in the infliximab trials was a PASI 75 response at 10 weeks, and that in the manufacturer's economic modelling it had been assumed that treatment would be discontinued if this response were not achieved at 10 weeks. • The Committee thought it appropriate for treatment to be continued beyond 10 weeks only in people whose psoriasis has shown a PASI 75 response to treatment within 10 weeks. • In addition, the Committee were persuaded that, for consistency, the response criteria should be defined in a similar way to TA103 (including a 50% reduction in the PASI score and a 5-point reduction in the DLQI) except that the

NICE TA	PASI response value used in cost-effectiveness modelling	Committee's preferred assumptions	Committee comments relating to PASI outcome
			assessment should made at 10 weeks after initiation of therapy.
TA103 (etanercept)[6]	• Manufacturer model: PASI 50 (efalizumab) • Assessment Group: PASI 75	• PASI 75, or PASI 50, plus at least 5-point reduction in DLQI from baseline, in line with clinical practice	• The Committee considered the most appropriate criteria for assessment of response to treatment. It was aware that the European Medicines Agency recognises that reduction of baseline PASI score by 75% (PASI 75) is an indicator that severe psoriasis has responded to treatment. • Additionally, the British Society for Rheumatology guidelines on the use of these agents in psoriatic arthritis also recommends collecting PASI data at baseline and using the PASI 75 as an indicator of response. • Therefore, the Committee considered that a criterion for adequacy of response should be the PASI 75 at 12 weeks as both etanercept and efalizumab were assessed at this time point.. • The Committee was however persuaded that the evidence and the expert testimony indicated that there were a number of individuals who, on the basis of assessment of improvement in quality of life, would derive significant benefit from etanercept or efalizumab, but might have failed to achieve a PASI 75 after 12 weeks of treatment. The Committee therefore considered that the assessment of response should also include a measure of quality of life improvement as defined by a change from the baseline DLQI at initiation of treatment. It concluded that it would also be appropriate for individuals to continue on treatment if they had achieved a PASI 50 response providing they had also achieved a 5-point reduction in their DLQI score from when treatment was initiated.
Key: DLQI, Dermatology Life Quality Index; NHS, National Health Service; PASI, Psoriasis Area Severity Index; TA, technology appraisal.			

Table 4: Discontinuation considered in previous relevant appraisals

NICE TA	Discontinuation used in cost-effectiveness modelling	Committee's preferred assumptions	Additional comments relating to discontinuation
TA442 (ixekizumab)[11]	• It was assumed that for people whose psoriasis responded to treatment, 20% stopped treatment each subsequent year	• The Committee did not discuss this	• The manufacturer supported their assumption using long-term data • The Committee did not discuss this
TA350 (secukinumab)[10]	• Within the annual Markov model and beyond year 1, the manufacturer assumed a 20% annual all-cause discontinuation probability, based on expert opinion	• The Committee considered that a probability of discontinuation of 20% may be an overestimate, but that this would affect all biological therapies, and was therefore likely to have a minimal impact upon the cost-effectiveness of secukinumab	• The ERG's clinical expert noted that a probability of discontinuation of 15% to 20% per year was a reasonable estimate for the proportion of patients who stop treatment annually beyond the first year. • The Committee considered the company's modelling assumption that 20% of all patients stop biological treatments each year, an assumption the company based on previous appraisals. The Committee heard from clinical experts that this was likely to be an overestimate because clinicians had an increasing number of treatments from which to choose. The Committee concluded that fewer patients stopped biologicals than had been assumed by the company but that, because this affected all biological treatments equally, it was likely to have a minimal effect on the cost-effectiveness of secukinumab.
TA180 (ustekinumab)[9]	• It was assumed that for people whose psoriasis responded to treatment, 20% stopped treatment	• The Committee heard that the estimate of 20% was considered reasonable	• The Committee heard from the clinical specialists that people on biological therapies do stop treatment because of a reduction in response or adverse events, and that they considered this estimate (20%) to be reasonable.

NICE TA	Discontinuation used in cost-effectiveness modelling	Committee's preferred assumptions	Additional comments relating to discontinuation
	each subsequent year		
TA146 (adalimumab)[8]	• The treatment period for each therapy (following a response) was taken from the York model, estimated using an annual drop-out of 20% for all patients	• The Committee did not discuss this	• The Committee did not discuss this
TA134 (infliximab)[7]	• The treatment period for each therapy (following a response) was taken from the York model, estimated using an annual drop-out of 20% for all patients	• The Committee considered that the manufacturer's estimate of 20% was reasonable	• The assumed annual drop-out rate in the model was considered by the ERG to be an underestimate because it was based on 6-month rather than annual data. The ERG postulated that the drop-out rate might be as high as 50%. • The Committee finally discussed the ERG's concerns over the drop-out for patients being given infliximab and the various inpatient costs. The Committee noted that the ERG's analysis had assumed a 50% drop-out over 12 months whereas the rate suggested by the manufacturer was 20% based on the York report. The Committee considered that the appropriate drop-out was likely to lie between these two estimates, particularly because the majority of drop-outs would occur in the first 6 months. Therefore, it accepted that the values adopted by the manufacturer were appropriate.
TA103 (etanercept)[6]	• Assessment Group assumed 20% discontinuation	• The Committee did not discuss this	• The Committee did not discuss this

Key: ERG, Evidence Review Group; TA, technology appraisal.

Table 5: Adverse event incidence considered in previous relevant appraisals

NICE TA	AE incidence used in cost-effectiveness modelling	Committee's preferred assumptions	Additional comments relating to AEs
TA442 (ixekizumab)[11]	• AEs were not included in the manufacturer's model	• The Committee would have preferred for costs of AEs to be included in the analysis; however, the Committee noted that the incidence of AEs was very small and that tolerability of ixekizumab was similar to other biological therapies	• The Committee was aware that the rates of serious AEs including non-melanoma skin cancer, malignancies other than non-melanoma skin cancer, and severe infection, were very low, and that most of the AEs related to treatment were mild to moderately severe and did not lead to stopping treatment. It heard from the clinical experts that serious infection was the main concern with biologicals, but that treatment was generally well tolerated. The committee concluded that the tolerability of ixekizumab was similar to that for other biological treatments approved for treating psoriasis. • However, the Committee considered that it was appropriate to capture all the benefits and costs, including the costs of AEs over the time horizon of the model. • The Committee concluded that the company should have included the costs of AEs in its economic model, particularly given that the quality of life data were likely to already include any disutility from AEs.
TA350 (secukinumab)[10]	• AEs were not included in the manufacturer's model	• The Committee noted that secukinumab was generally well tolerated, and given the evidence to date, concluded that secukinumab did not appear to be associated with AEs not already known for	• The ERG included the costs of serious AEs for patients taking biologicals for the first year, which the company had omitted from the model. • The Committee discussed the AEs associated with secukinumab, noting that it was generally tolerated, and that the events were consistent between the placebo, etanercept, and secukinumab 300mg and 150mg arms of the trials. The Committee was aware that, over time, real-world data on AEs will accumulate. Given the evidence to date, the Committee

NICE TA	AE incidence used in cost-effectiveness modelling	Committee's preferred assumptions	Additional comments relating to AEs
		biological treatments in general.	concluded that secukinumab did not appear to be associated with AEs not already known for biological treatments in general.
TA180 (ustekinumab)[9]	• AEs were not included in the manufacturer's model	• The Committee did not discuss this	• The Committee did not discuss this
TA146 (adalimumab)[8]	• AEs were not included in the manufacturer's model	• The Committee did not discuss this	• The Committee did not discuss this
TA134 (infliximab)[7]	• AEs were not included in the manufacturer's model	• The Committee did not discuss this	• The Committee did not discuss this
TA103 (etanercept)[6]	• AEs were not included in the manufacturer's or Assessment Group's models	• The Committee noted a lack of AE data for biological treatments	• The Committee considered the possibility of AEs with etanercept and efalizumab both in the short and longer term; it noted that there was currently little information on the use of these drugs in people with psoriasis beyond the duration of the RCTs. • The Committee agreed with the experts' advice that a register should be established in order to collect information on long-term outcomes (including adverse effects) in patients with psoriasis treated with cytokine inhibitors.
Key: AE, adverse event; ERG, Evidence Review Group; RCT, randomised controlled trial; TA, technology appraisal.			

B.2.2. Resource use assumptions

Resource use considered in previous relevant NICE technology appraisals includes administration, monitoring and best supportive care.

[redacted]

B.3. Clinical effectiveness

- The guselkumab clinical development programme is primarily composed of three regulatory Phase III RCTs that include >2,700 patients with moderate to severe plaque psoriasis.
- Guselkumab offers a new mode of action (IL-23 inhibitor) that delivers high and sustained levels of skin clearance with superior response compared to adalimumab.
  - In VOYAGE 1 and VOYAGE 2, guselkumab was superior to adalimumab for PASI 90 and PASI 75 at Week 16 and Week 24, and a higher proportion of patients achieved an IGA score of 0 at Week 16 and Week 24 ($p<0.001$).[53, 54]
  - In VOYAGE 1, guselkumab also showed superiority versus adalimumab at Week 48 for PASI 90, PASI 75 and IGA 0 ($p<0.001$) and demonstrated the ability to sustain clinical benefits through 2 years of continuous treatment.[53, 55]
- Guselkumab works in patients for whom ustekinumab provided an insufficient response and this is likely to result from its different mode of action.
  - In NAVIGATE, switching to guselkumab significantly increased the number of patients achieving an IGA score of 0/1 and ≥2-grade improvement at Week 28, compared to continuing ustekinumab ($p=0.001$).[56]

- Guselkumab has shown response in patients with regional psoriasis involvement (scalp, hands and feet) with significantly better results compared to placebo and adalimumab.
  - In VOYAGE 1 and VOYAGE 2, significantly more patients treated with guselkumab achieved ss-IGA and hf-PGA scores of 0/1 and ≥2 grade improvement at Week 16 compared to placebo ($p<0.001$) and at Week 24 compared to adalimumab ($p<0.05$).[53, 54]
- Guselkumab effectively normalises the impact of skin disease on the quality of life of an affected person compared to placebo and adalimumab and reduces comorbidities of anxiety and depression.
  - In VOYAGE 1 and VOYAGE 2, significantly more patients treated with GUS achieved DLQI 0/1 and PSSD 0 at Week 16 compared to placebo ($p<0.001$) and at Week 24 compared to adalimumab ($p<0.05$).[53, 54]
  - In VOYAGE 2, ~60% of patients with depression or anxiety reported no depression or anxiety (HADS <8) after 24 weeks of guselkumab treatment.
- Guselkumab is generally well tolerated with no new safety signals associated with the use of IL-23 inhibitor treatment observed.
  - In VOYAGE 1 and VOYAGE 2, the proportion of patients with SAEs was <5% across treatment groups and there were no events of tuberculosis, opportunistic infection or serious hypersensitivity.[53, 54]
  - In NAVIGATE, the proportion of patients with SAEs was <7% in both treatment arms and most SAEs reported were single events.[56]
- Conclusions of evidence from the head-to-head trial programme are replicated in a series of NMAs designed to compare the efficacy and safety of further biologic treatments relevant to the NHS (at the end of treatment induction).
  - Efficacy NMAs show that guselkumab is superior to anti-TNF, IL-12/23 ustekinumab and IL-17 secukinumab treatment, and non-inferior to IL-17 ixekizumab treatment.
  - Safety NMAs show that guselkumab has a similar safety profile to other biologics, regardless of treatment class.

B.3.1. Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.3.2. List of relevant clinical effectiveness evidence

The guselkumab clinical development programme is primarily composed of three regulatory Phase III randomised controlled trials (RCTs) that provide data for more than 2,700 patients with moderate to severe plaque psoriasis. These trials are summarised in Table 6 with further details of their design provided in Section B.3.3.

VOYAGE 1 provides evidence on the clinical benefits of guselkumab versus placebo (up to 16 weeks) and versus adalimumab (up to 48 weeks) in patients with moderate to severe plaque psoriasis, who were candidates for phototherapy or systemic treatment. VOYAGE 1 also provided evidence of the clinical benefits of continuing guselkumab longer-term (data available up to 100 weeks at this time). VOYAGE 2 provides evidence on the clinical benefits of guselkumab versus placebo (up to 16 weeks) and adalimumab (up to 24 weeks) in patients with moderate to severe plaque psoriasis, who were candidates for phototherapy or systemic treatment. VOYAGE 2 also provides evidence on the clinical benefits of continuing guselkumab treatments versus withdrawal of guselkumab treatment from Week 24 (up to 72 weeks) and on the clinical benefits of adalimumab non-responders switching to guselkumab. The VOYAGE studies are the pivotal trials providing data to support the use of guselkumab in NHS practice, and are the studies utilised in the network meta-analyses (NMA) and cost-comparison case.

NAVIGATE provides supportive evidence on the clinical benefits of guselkumab in patients with moderate to severe plaque psoriasis, who were candidates for phototherapy or systemic treatment and who have an inadequate response to ustekinumab. Data from this trial demonstrate the benefits of the new targeted IL-23 mode of action (compared with the IL-12/IL-23 mode of action associated with ustekinumab). Of note, the NAVIGATE trial did not meet the selection criteria for the systematic literature reviews (SLRs) described in Appendix D due to the open-label period where all patients received ustekinumab prior to randomisation.

Table 6: Clinical effectiveness evidence

Study	NCT02207231 (VOYAGE 1)	NCT02207244 (VOYAGE 2)	NCT02203032 (NAVIGATE)
Study design	Phase III, randomised, double-blind, multicentre, placebo- and active-comparator controlled trial.	Phase III, randomised, double-blind, multicentre, placebo- and active-comparator controlled trial with randomised withdrawal and retreatment.	Phase III, randomised, double-blind, multicentre, active-comparator controlled trial.
Population	Adult patients with a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study agent. Patients with non-plaque forms of psoriasis or with drug-induced psoriasis were excluded, as were patients who had ever previously received guselkumab or adalimumab.	Adult patients with a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study agent. Patients with non-plaque forms of psoriasis or with drug-induced psoriasis were excluded, as were patients who had ever previously received guselkumab or adalimumab.	Adult patients with a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study agent. Patients with non-plaque forms of psoriasis or with drug-induced psoriasis were excluded, as were patients who had ever previously received guselkumab or ustekinumab. All patients received open-label ustekinumab at Weeks 0 and 4, according to their weight at baseline (Week 0). At Week 16, patients with an inadequate response to ustekinumab (IGA≥2) were randomised to guselkumab or ustekinumab.
Intervention(s)	Guselkumab 100mg SC at Weeks 0, 4, 12 and q8w through to Week 44 (n=329).	Guselkumab 100mg SC at Weeks 0, 4, 12 and 20 (n=494). • PASI 90 non-responders continued guselkumab 100mg SC q8w (n=95). • Maintenance group (PASI 90 responders) continued guselkumab 100mg SC q8w (n=193). • Withdrawal group (PASI 90 responders) given placebo from	Guselkumab 100mg SC at Weeks 16, 20, and q8w until Week 44 (n=135).

Study	NCT02207231 (VOYAGE 1)	NCT02207244 (VOYAGE 2)	NCT02203032 (NAVIGATE)
		Week 28 until loss of ≥50% of the improvement in PASI achieved at Week 28, patients were re-treated with guselkumab 100mg SC, 4 weeks later and q8w (n=182).	
Comparator(s)	Placebo at Week 0, 4 and 12 followed by guselkumab 100mg at Week 16, 20 and q8w through to Week 44 (n=174). Adalimumab 80mg SC at Week 0, 40mg at Week 1 and q2w through to Week 47 (n=334).	Placebo SC at Week 0, 4 and 12 followed by guselkumab 100mg SC at Week 16, 20 (n=248). • PASI 90 non-responders continued guselkumab 100mg SC q8w (n=80). • PASI 90 responders given placebo from Week 28 until loss of ≥50% of the improvement in PASI achieved at Week 28, patients were re-treated with guselkumab 100mg SC, then 4 weeks later and q8w (n=147). Adalimumab 80mg at Week 0, 40mg at Week 1 and 40mg every q2w through to Week 23 (n=248). • PASI 90 non-responders given guselkumab 100mg SC at Week 28, 4 weeks later and q8w (n=112). • PASI 90 responders given placebo from Week 28 until loss of ≥50% of the improvement in PASI achieved at Week 28, patients were re-treated with guselkumab 100mg SC, then 4 weeks later and then q8w (n=116).	Ustekinumab (patients weighing ≤100kg: 45mg, patients weighing >100kg: 90mg) SC at Week 16 and q12w until Week 40 (n=133).

Study	NCT02207231 (VOYAGE 1)	NCT02207244 (VOYAGE 2)	NCT02203032 (NAVIGATE)
Does trial support application for marketing authorisation	Yes	Yes	Yes
Reported outcomes specified in the decision problem	• Severity of psoriasis • Psoriasis symptoms on the face, scalp and nails • Response and remission rate (as represented by skin clearance) • Relapse rate (as represented by loss of response) • Adverse effects of treatment • Health-related quality of life	• Severity of psoriasis • Psoriasis symptoms on the face, scalp and nails • Response and remission rate (as represented by skin clearance) • Relapse rate (as represented by loss of response) • Adverse effects of treatment • Health-related quality of life	• Severity of psoriasis • Psoriasis symptoms on the face, scalp and nails • Response and remission rate (as represented by skin clearance) • Relapse rate (as represented by loss of response) • Adverse effects of treatment • Health-related quality of life

Key: CSR, clinical study report; DLQI, Dermatology Quality of Life Index; f-PGA, Fingernail Physician Global Assessment; HADS, Hospital Anxiety and Depression Scale; hf-PGA, Physician Global Assessment of Hands and/or Feet; IGA, Investigator Global Assessment; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; PASI 50, 50% or greater improvement in PASI score from baseline; PASI 75, 75% or greater improvement in PASI score from baseline; PASI 90, 90% or greater improvement in PASI score from baseline; PASI 100, 100% improvement in PASI score from baseline; PsA, psoriatic arthritis; PSSD, Psoriasis Symptoms and Signs Diary; SC, subcutaneous; SF-36, Medical Outcomes Study 36-Item Short Form; ss-IGA, Scalp-Specific Investigator Global Assessment; q2w, every 2 weeks; q8w, every 8 weeks; q12w, every 12 weeks; WLQ, work life questionnaire.
Sources: Blauvelt *et al*., 2017[53]; VOYAGE 1 CSR[57]; Reich *et al*., 2017[54]; VOYAGE 2 CSR[58]; Langley *et al*., 2017[56]; NAVIGATE CSR[59].

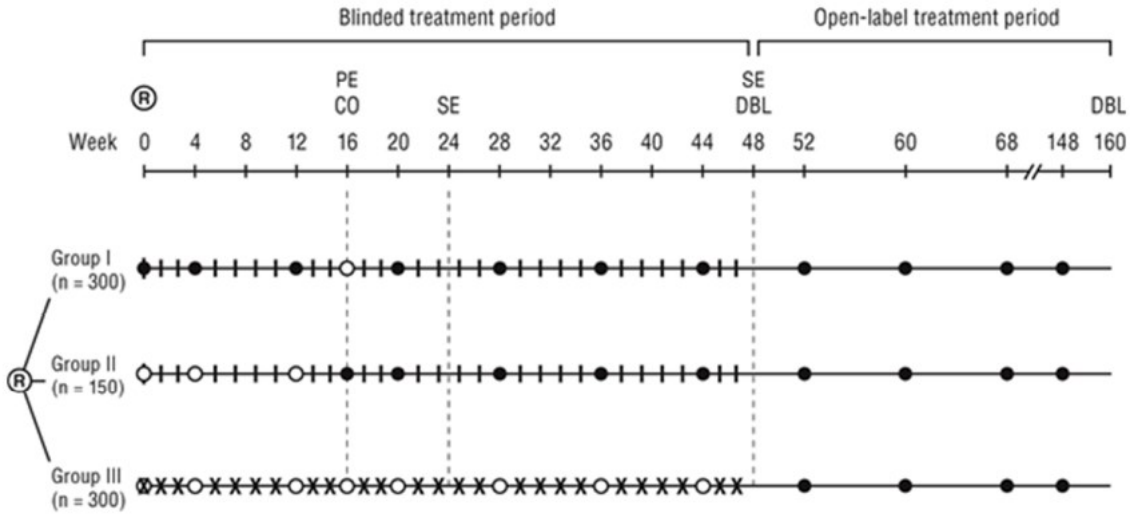
B.3.3. Summary of methodology of the relevant clinical effectiveness evidence

A comparative summary for the methodology of the three Phase III clinical trials, VOYAGE 1, VOYAGE 2 and NAVIGATE, are presented in Table 7.

VOYAGE 1

The VOYAGE 1 trial consisted of a double-blind treatment period (Weeks 0–48) and an open-label guselkumab treatment period (Weeks 48–160), as depicted in Figure 2. At Week 0 patients were randomised in a 2:1:2 ratio to guselkumab 100mg at Weeks 0, 4, 12 and every 8 weeks (q8w) through to Week 44 (Group I); placebo at Weeks 0, 4 and 12 followed by guselkumab 100mg at Weeks 16 and 20, and q8w through Week 44 (Group II); or adalimumab 80mg at Week 0, 40mg at Week 1, and 40mg every 2 weeks through Week 47 (Group III). After Week 48 patients in Groups I and II continued to receive guselkumab 100mg at Week 52 and q8w thereafter through to Week 148. Patients in Group III who were initially randomised to adalimumab entered a wash out period after their final dose of adalimumab at Week 47 and initiated guselkumab 100mg at Week 52 and then q8w thereafter through to Week 148.

Figure 2: Schematic overview of the of VOYAGE 1 trial



Key: ●, guselkumab 100mg; ○, placebo for guselkumab; X, adalimumab; I, placebo for adalimumab; R, randomisation; PE, primary endpoint; CO, placebo crossover; SE, secondary endpoint; DBL, database lock.
Source: VOYAGE 1 CSR.[57]

VOYAGE 2

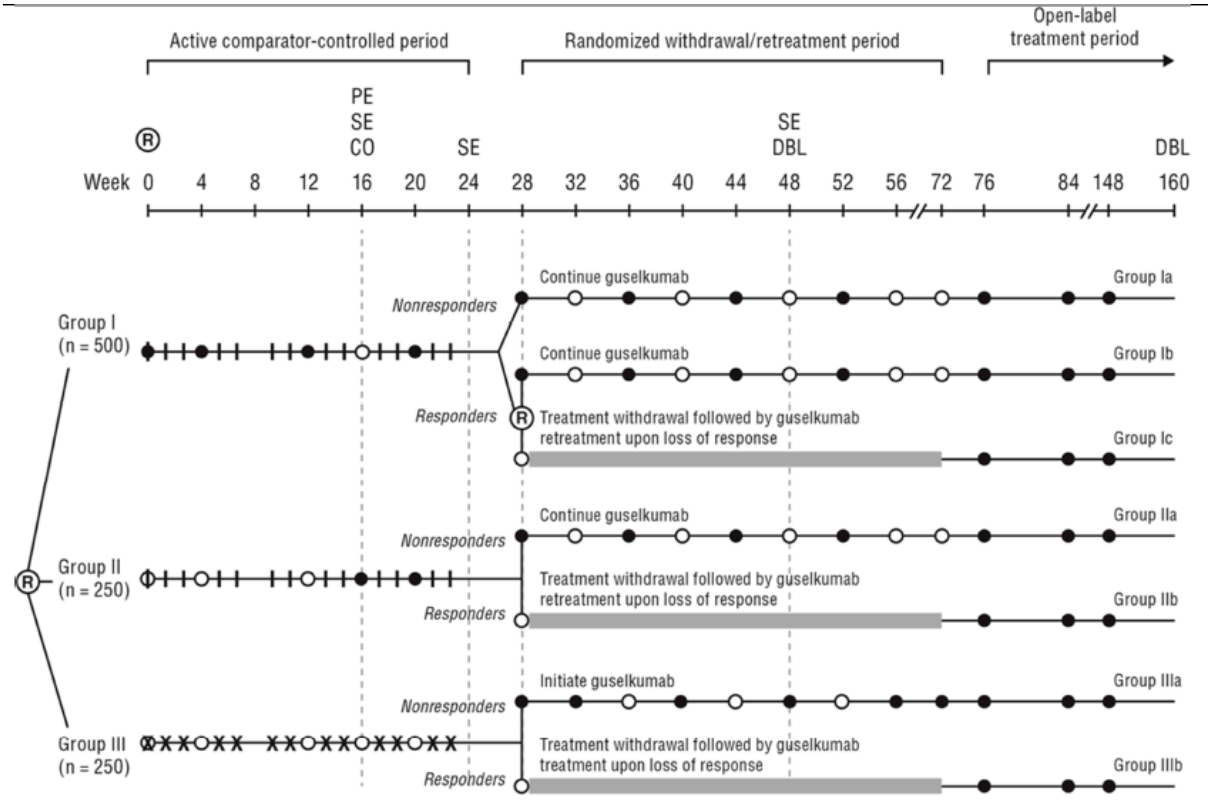
The VOYAGE 2 trial consisted of a double-blind treatment period (Weeks 0–24), a randomised withdrawal and retreatment period (Weeks 24–72) and an open-label guselkumab treatment period (Weeks 76–160), as depicted Figure 3. At Week 0, patients were randomised in a 2:1:1 ratio to guselkumab 100mg at Weeks 0, 4, 12 and 20 (Group I); placebo at Weeks 0, 4 and 12 followed by guselkumab 100mg at Weeks 16 and 20 (Group II); or adalimumab 80mg at Week 0, 40mg at Week 1, and 40mg every 2 weeks through Week 23 (Group III).

After Week 28 patients were re-treated based on their level of response at that visit. Patients in Group I who didn't achieve a 90% or greater improvement in PASI score from baseline (PASI 90), were classed as PASI 90 non-responders and continued guselkumab 100mg q8w. In contrast, patients who achieved a PASI 90 response were re-randomised in a 1:1 ratio to receive either guselkumab 100mg q8w through to Week 76 or placebo until a loss of 50% or more (≥50%) of the PASI improvement achieved at Week 28, at which point patients were re-treated with guselkumab 100mg followed by a 100mg dose 4 weeks later, and 100mg q8w thereafter through to Week 76.

Patients in Group II who were PASI 90 non-responders continued guselkumab 100mg q8w, whereas PASI 90 responders received placebo until a loss of ≥50% of the PASI improvement achieved at Week 28, at which point patients were re-treated with guselkumab 100mg followed by a 100mg dose 4 weeks later, and 100mg q8w thereafter through to Week 76.

Patients in Group III who were PASI 90 non-responders initiated guselkumab 100mg at Week 28 followed by a 100mg dose 4 weeks later, and then 100mg q8w thereafter through to Week 76, whereas PASI 90 responders received placebo until a loss of ≥50% of the improvement in PASI achieved at Week 28, at which point patients initiated guselkumab 100mg followed by a 100mg dose 4 weeks later, and then 100mg q8w through Week 76. At Week 76, all patients continued to receive guselkumab 100mg q8w through to Week 148.

Figure 3: Schematic overview of the VOYAGE 2 trial

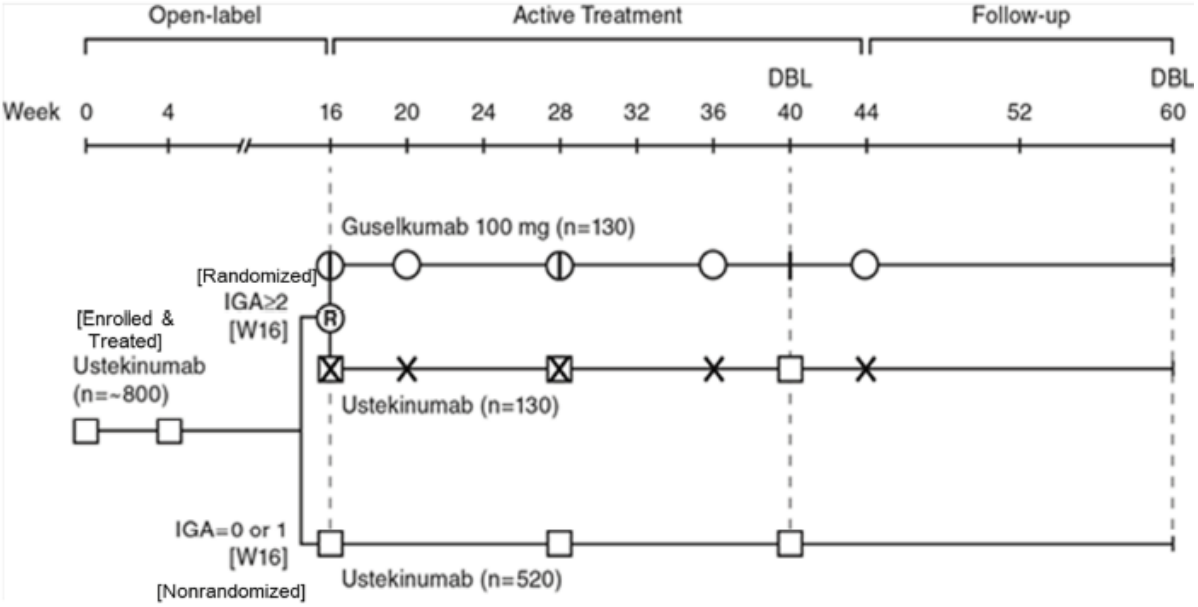


Key: ●, guselkumab 100mg; ○, placebo for guselkumab; X, adalimumab; I, placebo for adalimumab; R, randomisation; PE, primary endpoint; CO, placebo crossover; SE, secondary endpoint; DBL, database lock;
Source: VOYAGE 2 CSR.[58]

NAVIGATE

The NAVIGATE trial consisted of a 16-week open-label period, a 28-week randomised active-treatment period, and a 16-week follow-up period, as depicted in Figure 4. All patients received open-label ustekinumab at Weeks 0 and 4 according to their baseline weight (≤100kg: 45mg dose, >100kg: 90mg dose). At Week 16, patients were randomised based on their response to ustekinumab. Patients with an inadequate response to ustekinumab (IGA score ≥2) were randomised to either switch to guselkumab 100mg at Weeks 16 and 20 and then q8w thereafter or continue ustekinumab every 12 weeks (q12w) through Week 44. In contrast, patients with an IGA 0/1 continued to receive open-label ustekinumab q12w through Week 44. Patients were followed for efficacy through Week 52 and safety through Week 60.

Figure 4: Schematic overview of the of the NAVIGATE trial



Key: ○**,** guselkumab 100mg; ☐, ustekinumab; X, placebo for guselkumab; I, placebo for ustekinumab; R, randomisation; DBL, database lock; IGA, Investigators Global Assessment; W, Week;
Source: NAVIGATE CSR.[59]

Table 7: Comparative summary of trial methodology

Study	NCT02207231 (VOYAGE 1)	NCT02207244 (VOYAGE 2)	NCT02203032 (NAVIGATE)
Location	101 sites in 10 countries: Canada, USA, Hungary, Poland, Russia, Germany, Spain, Australia, South Korea and Taiwan.	115 sites in nine countries: USA, Canada, Poland, Czech Republic, Germany, Spain, Russia, Australia, and South Korea.	100 sites in 10 countries: USA, Canada, Germany, Poland, Russia, Spain, Australia, South Korea, UK and Taiwan.
Trial design	Phase III, randomised, double-blind, multicentre, placebo- and active-comparator controlled trial; Week 16 crossover from placebo to GUS. Permuted block randomisation with stratification by investigator site was used. Central randomisation was implemented using an interactive World Wide Web response system.	Phase III, randomised, double-blind, multicentre, placebo- and active-comparator controlled trial; Week 16 crossover from placebo to GUS; Week 28 study continuation or withdrawal. Permuted block randomisation with stratification by investigator site was used. Central randomisation occurred using an interactive web based response system.	Phase III, randomised, double-blind, multicentre trial; open-label ustekinumab for 16 weeks, then continuation on ustekinumab or crossover to GUS. Randomisation was performed using an interactive web response system with patients stratified by baseline weight (≤100kg vs >100kg) and study site.
Eligibility criteria for participants	Inclusion criteria included: • Man, or woman ≥18 years of age. • Diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study agent. • PASI ≥12, IGA ≥3, and involved BSA ≥10% at screening and at baseline. • Prior candidate for phototherapy or systemic treatment for psoriasis. • In addition, patients had to meet criteria for: - Concomitant medication stability	Inclusion criteria included: • Man, or woman ≥18 years of age. • Diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study agent. • PASI ≥12, IGA ≥3, and involved BSA ≥10% at screening and at baseline. • Prior candidate for phototherapy or systemic treatment for psoriasis. • In addition, patients had to meet criteria for: - Concomitant medication stability	Inclusion criteria included: • Man, or woman ≥18 years of age. • Diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study agent. • PASI ≥12, IGA ≥3, and involved BSA ≥10% at screening and at baseline. • Prior candidate for phototherapy or systemic treatment for psoriasis. • In addition, patients had to meet criteria for: - Concomitant medication stability

Study	NCT02207231 (VOYAGE 1)	NCT02207244 (VOYAGE 2)	NCT02203032 (NAVIGATE)
	- Screening laboratory test results - TB history and testing results - Agree to use adequate birth control measures - Avoid prolonged sun exposure - Avoid use of tanning booths or other ultraviolet light sources during study Exclusion criteria were: • Non-plaque form of psoriasis or possible drug-induced psoriasis • Prior treatment with guselkumab or adalimumab • Prior treatment with any of the following therapeutic agents: - Agents targeted at reducing IL-12, IL-17, or IL-23 - Agents that modulate B cells or T cells - Anti-TNFα biological therapy - Systemic immunosuppressants - Phototherapy or any systemic or topical medications/treatments that could affect psoriasis or IGA evaluations - Lithium, antimalarials, or intramuscular gold - Experimental antibodies or biologic therapy	- Screening laboratory test results - TB history and testing results - Agree to use adequate birth control measures - Avoid prolonged sun exposure - Avoid use of tanning booths or other ultraviolet light sources during study Exclusion criteria were: • Non-plaque form of psoriasis or possible drug-induced psoriasis • Prior treatment with guselkumab or adalimumab. • Prior treatment with any of the following therapeutic agents: - Agents targeted at reducing IL-12, IL-17, or IL-23 - Agents that modulate B cells or T cells - Anti-TNFα biological therapy - Systemic immunosuppressants - Phototherapy or any systemic or topical medications/treatments that could affect psoriasis or IGA evaluations - Lithium, antimalarials, or intramuscular gold - Experimental antibodies or biologic therapy	- Screening laboratory test results - TB history and testing results - Agree to use adequate birth control measures - Avoid prolonged sun exposure - Avoid use of tanning booths or other ultraviolet light sources during study Exclusion criteria were: • Non-plaque form of psoriasis or possible drug-induced psoriasis • Prior treatment with guselkumab or adalimumab. • Prior treatment with any of the following therapeutic agents: - Agents targeted at reducing IL-12, IL-17, or IL-23 - Agents that modulate B cells or T cells - Anti-TNFα biological therapy - Systemic immunosuppressants - Phototherapy or any systemic or topical medications/treatments that could affect psoriasis or IGA evaluations - Lithium, antimalarials, or intramuscular gold - Experimental antibodies or biologic therapy

Study	NCT02207231 (VOYAGE 1)	NCT02207244 (VOYAGE 2)	NCT02203032 (NAVIGATE)
	- Any other experimental therapy or new investigational agent were prohibited within specified time periods before the first administration of study agent • Received Bacille Calmette-Guérin vaccination or any live viral or bacterial vaccination within specified time periods before screening or the first administration of study agent, respectively. • Not agreed to not receive a live virus or live bacterial vaccination during the study, or within 3 months after the last administration of study agent. • Prior or current treatment with allergy immunotherapy for prevention of anaphylactic reactions. • Experienced a serious infection or herpes zoster within specified time periods before screening. • Evidence of current active infection or a history of latent or active granulomatous infection (including TB), nontuberculous mycobacterial infection, serious opportunistic infection, chronic or recurrent infectious disease, or	- Any other experimental therapy or new investigational agent were prohibited within specified time periods before the first administration of study agent • Received Bacille Calmette-Guérin vaccination or any live viral or bacterial vaccination within specified time periods before screening or the first administration of study agent, respectively. • Not agreed to not receive a live virus or live bacterial vaccination during the study, or within 3 months after the last administration of study agent. • Prior or current treatment with allergy immunotherapy for prevention of anaphylactic reactions. • Experienced a serious infection or herpes zoster within specified time periods before screening. • Evidence of current active infection or a history of latent or active granulomatous infection (including TB), nontuberculous mycobacterial infection, serious opportunistic infection, chronic or recurrent infectious disease, or	- Any other experimental therapy or new investigational agent were prohibited within specified time periods before the first administration of study agent • Received Bacille Calmette-Guérin vaccination or any live viral or bacterial vaccination within specified time periods before screening or the first administration of study agent, respectively. • Not agreed to not receive a live virus or live bacterial vaccination during the study, or within 3 months after the last administration of study agent. • Prior or current treatment with allergy immunotherapy for prevention of anaphylactic reactions. • Experienced a serious infection or herpes zoster within specified time periods before screening. • Evidence of current active infection or a history of latent or active granulomatous infection (including TB), nontuberculous mycobacterial infection, serious opportunistic infection, chronic or recurrent infectious disease, or

Study	NCT02207231 (VOYAGE 1)	NCT02207244 (VOYAGE 2)	NCT02203032 (NAVIGATE)
	infection with HIV, hepatitis B, or hepatitis C. • History of malignancy (except for a treated nonmelanoma skin cancer or treated cervical carcinoma *in situ* within specified time periods before the first study agent administration). • Diagnosis or history of lymphoproliferative disease. • Presence of severe, progressive, or uncontrolled renal, hepatic, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric or metabolic disturbances. • Unstable cardiovascular disease. • Organ transplantation. • Known substance abuse. • Pregnancy, planning a pregnancy (both men and women) within 5 months following the last administration of study agent, or currently nursing.	infection with HIV, hepatitis B, or hepatitis C. • History of malignancy (except for a treated nonmelanoma skin cancer or treated cervical carcinoma *in situ* within specified time periods before the first study agent administration). • Diagnosis or history of lymphoproliferative disease. • Presence of severe, progressive, or uncontrolled renal, hepatic, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric or metabolic disturbances. • Unstable cardiovascular disease. • Organ transplantation. • Known substance abuse. • Pregnancy, planning a pregnancy (both men and women) within 5 months following the last administration of study agent, or currently nursing.	infection with HIV, hepatitis B, or hepatitis C. • History of malignancy (except for a treated nonmelanoma skin cancer or treated cervical carcinoma *in situ* within specified time periods before the first study agent administration). • Diagnosis or history of lymphoproliferative disease. • Presence of severe, progressive, or uncontrolled renal, hepatic, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric or metabolic disturbances. • Unstable cardiovascular disease. • Organ transplantation. • Known substance abuse. • Pregnancy, planning a pregnancy (both men and women) within 5 months following the last administration of study agent, or currently nursing.

Study	NCT02207231 (VOYAGE 1)	NCT02207244 (VOYAGE 2)	NCT02203032 (NAVIGATE)
Settings and location where the data were collected	Instructions for the collection, handling, storage, and shipment of samples to a central laboratory for blinded analyses were provided to each site. A DMC was established to monitor data on an ongoing basis to ensure the continuing safety of patients.	Instructions for the collection, handling, storage, and shipment of samples to a central laboratory for blinded analyses were provided to each site. A DMC was established to monitor data on an ongoing basis to ensure the continuing safety of patients.	Instructions for the collection, handling, storage, and shipment of samples to a central laboratory for blinded analyses were provided to each site. A DMC was established to monitor data on an ongoing basis to ensure the continuing safety of patients.
Trial drugs	• **Group I:** Guselkumab 100mg SC dose at Weeks 0, 4, 12 and q8w through to Week 44 (n=329). • **Group II:** Placebo SC dose at Weeks 0, 4 and 12 followed by guselkumab 100mg at Week 16, 20 and q8w through to Week 44 (n=147). • **Group III:** Adalimumab 80mg SC dose at Week 0 and 40mg SC dose at Week 1 and q2w through to Week 47 (n=333).	**Weeks 0–28** • **Group I:** Guselkumab 100mg SC dose at Weeks 0, 4, 12 and 20 (n=496). • **Group II:** Placebo SC dose at Week 0, 4 and 12 followed by guselkumab 100mg SC dose at Week 16, 20 (n=248). • **Group III:** Adalimumab 80mg SC dose at Week 0 and 40mg SC dose at Week 1 and q2w through to Week 23 (n=248). **Weeks 28–72** • **Group I** was re-treated as follows: • PASI 90 non-responders continued guselkumab 100mg q8w (n=95). • PASI 90 responders were randomised to: – Continue guselkumab 100mg q8w (n=193) – Placebo from Week 28 until loss of ≥50% of the improvement in	**Weeks 0–16** • All patients received open-label ustekinumab (patients weighing ≤100kg: 45mg SC dose, patients weighing >100kg: 90mg SC dose) at Weeks 0 and 4 (n=871). **Weeks 16–60** • Patients with an IGA ≥2 were randomised to: - Guselkumab 100mg SC dose at Weeks 16, 20, and q8w until Week 44 (n=135) - Continue receiving open label ustekinumab q12w until Week 40 (n=133) • Patients with an IGA of 0 or 1 continued receiving open-label ustekinumab q12w until Week 40 (n=585)

Study	NCT02207231 (VOYAGE 1)	NCT02207244 (VOYAGE 2)	NCT02203032 (NAVIGATE)
		PASI achieved at Week 28, patients were re-treated with guselkumab 100mg, then 4 weeks later and q8w (n=182). **Group II** were re-treated as follows: • PASI 90 non-responders continued guselkumab 100mg q8w (n=80). • PASI 90 responders given placebo from Week 28 until loss of ≥50% of the improvement in PASI achieved at Week 28, patients were re-treated with guselkumab 100mg, then 4 weeks later and q8w (n=147). **Group III** were re-treated as follows: • PASI 90 non-responders given guselkumab 100mg at Week 28, 4 weeks later and q8w (n=112). • PASI 90 responders given placebo from Week 28 until loss of ≥50% of the improvement in PASI achieved at Week 28, patients were re-treated with guselkumab 100mg, then 4 weeks later and then q8w (n=116).	
Permitted and disallowed concomitant medication	The use of phototherapy or systemic anti-psoriatic medications including alternative biologics were not permitted at any time during the study.	The use of phototherapy or systemic anti-psoriatic medications including alternative biologics were not permitted at any time during the study.	The use of phototherapy, systemic anti-psoriatic medications including alternative biologics, and topical therapies that could affect psoriasis or the IGA evaluation were not permitted

Study	NCT02207231 (VOYAGE 1)	NCT02207244 (VOYAGE 2)	NCT02203032 (NAVIGATE)
	Topical therapies that could affect psoriasis or the IGA evaluation were not permitted during Week 0 through Week 48 but with the exception of ultra-high potency corticosteroids were allowed from Week 48. Concomitant medications for conditions other than psoriasis were kept stable throughout the study wherever possible. Stable doses of non-disease-modifying NSAIDs were allowed; the use of corticosteroids was limited to situations for which there were no adequate alternatives.	Topical therapies that could affect psoriasis or the IGA evaluation were not permitted during Week 0 through Week 48 but with the exception of ultra-high potency corticosteroids were allowed from Week 48. Concomitant medications for conditions other than psoriasis were kept stable throughout the study wherever possible. Stable doses of non-disease-modifying NSAIDs were allowed; the use of corticosteroids was limited to situations for which there were no adequate alternatives.	at any time during the study. If a prohibited medication is administered during the open-label or blinded-active treatment phases (i.e. Week 0 through Week 44), the patient was discontinued; if a prohibited medication is administered during the follow-up phase (i.e. Week 44 through Week 60), the patient completed the final study visit (Week 60) and the medication recorded. Concomitant medications for conditions other than psoriasis were kept stable throughout the study wherever possible. Stable doses of non-disease-modifying NSAIDs were allowed; the use of corticosteroids was limited to situations for which there were no adequate alternatives.
Primary outcome	The two co-primary efficacy endpoints, comparing the guselkumab group and the placebo group were: • Proportion of patients who achieved IGA 0/1 at Week 16 • Proportion of patients who achieved PASI 90 response at Week 16	The two co-primary efficacy endpoints, comparing the guselkumab group and the placebo group were: • Proportion of patients who achieved IGA 0/1 at Week 16 • Proportion of patients who achieved PASI 90 response at Week 16	The primary endpoint was the number of visits at which patients achieved an IGA response of 0/1 and a ≥2-grade improvement (from Week 16) between Week 28 and Week 40 among randomised patients with an inadequate response to ustekinumab (IGA≥2) at Week 16.

Study	NCT02207231 (VOYAGE 1)	NCT02207244 (VOYAGE 2)	NCT02203032 (NAVIGATE)
Major secondary outcomes	• Major secondary endpoints, comparing the guselkumab group and the placebo group included: • Change from baseline in DLQI score at Week 16 • Proportion of patients who achieved an ss-IGA score of 0/1 at Week 16 • Change from baseline in PSSD symptom score at Week 16 Major secondary endpoints, comparing the guselkumab group and the adalimumab group included: • Proportion of patients who achieved IGA 0 at Week 24 • Proportion of patients who achieved IGA score of 0/1 at Week 24 • Proportion of patients who achieved PASI 90 at Week 24 • Proportion of patients who achieved an IGA 0 at Week 48 • Proportion of patients who achieved an IGA score of 0/1 at Week 48 • Proportion of patients who achieved a PASI 90 at Week 48 • Proportion of patients who achieved an IGA score of 0/1 at Week 16 • Proportion of patients who achieved a PASI 90 at Week 16 • Proportion of patients who achieved	• Major secondary endpoints, comparing the guselkumab group and the placebo group included: • Time to loss of PASI 90 through Week 48 from Week 28 • Change from baseline in DLQI score at Week 16 • Proportion of patients who achieve an ss-IGA 0/1 at Week 16 • Change from baseline in PSSD symptom score at Week 16 Major secondary endpoints, comparing the guselkumab group and the adalimumab group included: • Proportion of patients who achieved IGA 0 at Week 24 • Proportion of patients who achieved IGA 0/1 at Week 24 • Proportion of patients who achieved PASI 90 at Week 24 • Proportion of patients who achieved an IGA 0/1 at Week 16 • Proportion of patients who achieved a PASI 90 at Week 16 • Proportion of patients who achieved a PASI 75 at Week 16 • Proportion of patients who achieved a PSSD symptom score=0 at Week 24	Major secondary endpoints included: • The number of visits to achieve a PASI 90 Response from Week 28 through Week 40 • The number of visits to achieve an IGA response of 0 from Week 28 through Week 40 • The proportion of patients who achieved an IGA of 0/1 and ≥2-grade improvement (from Week 16) at Week 28

Study	NCT02207231 (VOYAGE 1)	NCT02207244 (VOYAGE 2)	NCT02203032 (NAVIGATE)
	a PASI 75 at Week 16 • Proportion of patients who achieved a PSSD symptom score=0 at Week 24		
Pre-planned subgroups	• To evaluate the consistency of efficacy as measured by the co-primary endpoints and select major secondary endpoints in different subpopulations, subgroup analyses were performed based on baseline demographic characteristics, baseline disease characteristics, and psoriasis medication history. Subgroup analyses were planned when the number of patients in the subgroups permitted.	To evaluate the consistency of efficacy as measured by the co-primary endpoints and selected major secondary endpoints (IGA score of 0, IGA 0/1, and PASI 90 responses at Week 24) in different subpopulations, subgroup analyses were performed based on baseline demographic characteristics, baseline disease characteristics, and psoriasis medication history in addition, PASI and IGA responses by weight over time were summarised. Subgroup analyses were planned when the number of patients in the subgroups permitted.	To evaluate the consistency of efficacy as measured by the primary endpoint in different subpopulations, subgroup analyses were performed based on demographic characteristics, baseline disease characteristics, and psoriasis medication history. Subgroup analyses were planned when the number of patients in the subgroups permitted.

Key: BSA, body surface area; CFB, change from baseline; CSR, clinical study report; DLQI, Dermatology Quality of Life Index; DMC, data monitoring committee; GUS, guselkumab; f-PGA, Fingernail Physician Global Assessment; HADS, Hospital Anxiety and Depression Scale; hf-PGA, Physician Global Assessment of Hands and/or Feet; HIV, human immunodeficiency virus; IGA, Investigator Global Assessment; IL, interleukin; MSC, Mental Component Score; NA, not applicable; NAPSI, Nail Psoriasis Severity Index; NSAID, nonsteroidal anti-inflammatory drug; PASI, Psoriasis Area and Severity Index; PASI 50, 50% or greater improvement in PASI score from baseline; PASI 75, 75% or greater improvement in PASI score from baseline; PASI 90, 90% or greater improvement in PASI score from baseline; PASI 100, 100% improvement in PASI score from baseline; PSC, Physical Component Score; PsA, psoriatic arthritis; PSSD, Psoriasis Symptoms and Signs Diary; every 2 weeks; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; SF-36, Medical Outcomes Study 36-Item Short Form; ss-IGA, Scalp-Specific Investigator Global Assessment; TB, tuberculosis; TNF, tumour necrosis factor; UST, ustekinumab; WLQ, work life questionnaire.
Notes: [a], Tested for superiority of the guselkumab group compared with the placebo group.
Source: VOYAGE 1 CSR[57]; VOYAGE 2 CSR[58]; NAVIGATE CSR[59]

Baseline characteristics

Baseline demographics and clinical characteristics of patients were well balanced across treatment groups and were generally similar across studies.

In line with the eligibility criteria, all patients had a PASI score of ≥12, IGA ≥3 and involved BSA ≥10% at baseline; however, the mean PASI score was ≥20, the mean involved BSA was ≥25%, and the mean DLQI was approximately 14 across groups, suggesting that at baseline, patients were at the more severe disease stage than the moderate disease stage. The majority of patients in the VOYAGE trials also had regional psoriasis at the scalp (approximately 80%) and nails (approximately 55%); approximately 25% of patients also had regional psoriasis at the hands and/or feet.

With regard to treatment history, most patients in the VOYAGE trials had received topical agents (approximately 90%) as we would expect in line with the eligibility criteria of patients who were candidates for phototherapy or systemic treatment. Many patients had also received previous phototherapy (approximately 55%) and conventional systemic therapy (non-biologic) (approximately 60%). Approximately 20% of patients had received previous biologic treatment. At the time of randomisation in NAVIGATE, all patients had received previous biologic treatment.

Baseline characteristics for VOYAGE 1 and VOYAGE 2 are summarised in Table 8 and baseline characteristics for NAVIGATE are summarised in Table 9.

Table 8: Baseline characteristics of patients in VOYAGE 1 and VOYAGE 2

Study	NCT02207231 (VOYAGE 1)			NCT02207244 (VOYAGE 2)		
Treatment	**Placebo**	**Guselkumab**	**Adalimumab**	**Placebo**	**Guselkumab**	**Adalimumab**
Dose/schedule	PBO SC at Week 0, 4 and 12, GUS 100mg SC Week 16, 20 q8w	100mg SC Week 0, 4, 12 and q8w to Week 44	80mg SC at Week 0, 40mg Week 1 and q2w to Week 47	PBO SC at Week 0, 4 and 12, GUS 100mg SC Week 16, 20	100mg SC Week 0, 4, 12 and 20	80mg SC at Week 0, 40mg Week 1 and q2w to Week 23
Patients, n	174	329	333	248	496	248
Age, years, mean (SD)	44.9 (12.90)	43.9 (12.74)	42.9 (12.58)	43.3 (12.4)	43.7 (12.2)	43.2 (11.9)
Sex, male, n (%)	119 (68.4)	240 (72.9)	249 (74.6)	173 (69.8)	349 (70.4)	170 (68.5)
Race, n (%)						
White	145 (83.3)	262 (79.6)	277 (82.9)	206 (83.1)	408 (82.3)	200 (80.6)
Asian	23 (13.2)	51 (15.5)	47 (14.1)	27 (10.9)	72 (14.5)	37 (14.9)
Black	3 (1.7)	6 (1.8)	8 (2.4)	8 (3.2)	6 (1.2)	5 (2.0)
BMI, kg/m^2						
Mean (SD)	28.9 (6.89)	29.7 (6.22)	29.8 (6.48)	29.6 (6.6)	29.6 (6.5)	29.6 (6.6)
Median (IQR)	27.3 (24.1–33.1)	28.7 (25.5–32.9)	28.7 (25.2–33.5)	28.4 (25.2–33.4)	28.5 (25.5–32.6)	28.3(25.1–33.1)
Duration of psoriasis, years, mean (SD)	17.6 (12.44)	17.9 (12.27)	17.0 (11.27)	17.9 (11.9)	17.9 (12.0)	17.6 (11.7)
% Body surface area involvement, mean (SD)	25.8 (15.9)	28.3 (17.1)	28.6 (16.7)	28.0 (16.5)	28.5 (16.4)	29.1 (16.7)
IGA score (0–4), n (%)						
Mild, 2	0	0	3 (0.9)	0	1 (0.2)	0
Moderate, 3	131 (75.3)	252 (76.6)	241 (72.2)	191 (77.0)	380 (76.6)	195 (78.6)
Severe, 4	43 (24.7)	77 (23.4)	90 (26.9)	57 (23.0)	115 (23.2)	53 (21.4)

Study	NCT02207231 (VOYAGE 1)			NCT02207244 (VOYAGE 2)		
Treatment	**Placebo**	**Guselkumab**	**Adalimumab**	**Placebo**	**Guselkumab**	**Adalimumab**
PASI score, 0–72						
Mean (SD)	20.4 (8.74)	22.1 (9.49)	22.4 (8.97)	21.5 (8.0)	21.9 (8.8)	21.7 (9.0)
Median (IQR)	17.4 (14.4–23.1)	18.6 (15.6–25.5)	20.0 (16.0–26.1)	19.0 (15.7–25.2)	19.2 (15.3–25.8)	19.0 (15.3–25.7)
ss-IGA score, 0–4, n (%)	150 (86.2)	291 (88.4)	295 (88.3)	212 (85.5)	423 (85.3)	205 (82.7)
Absence of disease, 0	0	0	0	0	0	0
Very mild, 1	5 (3.3)	14 (4.8)	9 (3.1)	10 (4.7)	15 (3.5)	11 (5.4)
Mild, 2	31 (20.7)	49 (16.8)	54 (18.3)	33 (15.6)	80 (18.9)	43 (21.0)
Moderate, 3	89 (59.3)	171 (58.8)	175 (59.3)	133 (62.7)	267 (63.1)	118 (57.6)
Severe, 4	25 (16.7)	57 (19.6)	57 (19.3)	36 (17.0)	61 (14.4)	33 (16.1)
f-PGA score, 0–4, n (%)	99 (56.9)	198 (60.2)	194 (58.1)	139 (56.0)	280 (56.5)	139 (56.0)
Cleared, 0	0	0	0	0	0	0
Minimal, 1	11 (11.1)	24 (12.1)	21 (10.8)	16 (11.5)	34 (12.1)	15 (10.8)
Mild, 2	33 (33.3)	62 (31.3)	66 (34.0)	40 (28.8)	92 (32.9)	51 (36.7)
Moderate, 3	42 (42.4)	83 (41.9)	90 (46.4)	65 (46.8)	122 (43.6)	59 (42.4)
Severe, 4	13 (13.1)	29 (14.6)	17 (8.8)	18 (12.9)	32 (11.4)	14 (10.1)
NAPSI score, 0–8, n (%)	99 (56.9)	194 (59.0)	191 (57.2)	140 (56.5)	280 (56.5)	140 (56.5)
Mean (SD)	4.7 (1.9)	4.9 (2.0)	4.6 (2.0)	5.0 (2.0)	4.8 (2.0)	4.5 (1.9)
hf-PGA score, 0–4, n (%)	44 (25.3)	100 (30.4)	101 (30.2)	67 (27.0)	127 (25.6)	62 (25.0)
Cleared, 0	0	0	0	0	0	0
Almost cleared, 1	1 (2.3)	10 (10.0)	6 (5.9)	4 (6.0)	13 (10.2)	6 (9.7)
Mild, 2	15 (34.1)	34 (34.0)	37 (36.6)	23 (34.3)	43 (33.9)	17 (27.4)
Moderate, 3	21 (47.7)	42 (42.0)	45 (44.6)	35 (52.2)	58 (45.7)	32 (51.6)
Severe, 4	7 (15.9)	14 (14.0)	13 (12.9)	5 (7.5)	13 (10.2)	7 (11.3)
Psoriatic arthritis, n (%)	30 (17.2)	64 (19.5)	62 (18.6)	46 (18.5)	89 (17.9)	44 (17.7)

Study	NCT02207231 (VOYAGE 1)			NCT02207244 (VOYAGE 2)		
Treatment	**Placebo**	**Guselkumab**	**Adalimumab**	**Placebo**	**Guselkumab**	**Adalimumab**
Prior treatments, n (%)						
Topical agents	154 (88.5)	299 (90.9)	309 (92.8)	233 (94.0)	477 (96.2)	237 (96.0)
Phototherapy	86 (49.4)	188 (57.3)	180 (53.9)	137 (55.2)	293 (59.1)	135 (54.7)
Conventional systemic agents	92 (52.9)	210 (63.8)	215 (64.4)	149 (60.1)	331 (66.7)	159 (64.1)
Biologic agents	34 (19.5)	71 (21.6)	70 (21.0)	54 (21.8)	101 (20.4)	49 (19.8)
SF-36 (0–100), n	NR	NR	NR	248	494	246
PCS score						
Mean (SD)	NR	NR	NR	47.3 (9.5)	47.5 (9.2)	48.9 (8.5)
Median	NR	NR	NR	49.0	49.1	50.0
MCS score						
Mean (SD)	NR	NR	NR	45.0 (11.3)	44.3 (11.5)	43.9 (11.5)
Median	NR	NR	NR	46.0	46.1	45.4
DLQI score (0–30), n	170	322	328	248	495	247
Mean (SD)	13.3 (7.12)	14.0 (7.48)	14.4 (7.29)	15.1 6 7.2	14.7 (6.9)	15.0 (6.9)
PSSD score (0–100), n	129	249	274	198	411	201
Symptom score, mean (SD)	48.3 (23.77)	54.4 (24.63)	53.9 (25.79)	60.9 (20.2)	56.3 (22.5)	56.8 (21.5)
Sign score, mean (SD)	53.6 (20.34)	56.9 (21.30)	58.5 (21.73)	58.6 (23.6)	54.2 (26.1)	53.8 (26.1)

Key: BMI, body max index; CSR, clinical study report; DLQI, Dermatology Life Quality Index; f-PGA, Fingernail Physician Global Assessment; GUS, guselkumab; hf-PGA, Physician Global Assessment of hands and/or feet; IGA, Investigator Global Assessment ; IQR, interquartile range; MCS, Mental Component Score; NAPSI, Nail Psoriasis Severity Index; NR, not reported; PASI, Psoriasis Severity Index; PBO, placebo; PCS, Physical Component Score; PSSD, Psoriasis Symptoms and Signs Diary; q2w, every 2 weeks; q8w, every 8 weeks; SC, subcutaneous; SD, standard deviation; SF-36, Medical Outcomes Study 36-iten Short Form; ss-IGA, scalp-specific Investigator Global Assessment.
Source: VOYAGE 1 CSR[57], VOYAGE 2 CSR[58]

Table 9: Baseline characteristics of patients in NAVIGATE

Study	**NCT02203032 (NAVIGATE)**			
	All patients	**Nonrandomised**	**Patients randomised at Week 16**	
Treatment	**Open-label ustekinumab run-in**	**Open-label ustekinumab continuation**	**Guselkumab**	**Ustekinumab**
Dose/schedule	Ustekinumab 45mg SC dose (≤100kg) or 90mg SC dose (>100kg) at Weeks 0 and 4	Ustekinumab 45mg SC dose (≤100kg) or 90mg SC dose (>100kg) e12w until Week 40	Guselkumab 100mg SC dose at Weeks 16, 20, and eq8w until Week 44	Ustekinumab 45mg SC dose (≤100kg) or 90mg SC dose (>100kg) e12w until Week 40
Patients, n	**871**	**585**	**135**	**133**
Age, years, mean (SD)	43.1 (13.2)	42.9 (13.1)	44.2 (13.4)	43.0 (13.7)
Sex, male, n (%)	566 (65.0)	372 (63.6)	95 (70.4)	88 (66.2)
Race, n (%)				
White	747 (85.8)	523 (89.4)	109 (80.7)	99 (74.4)
Asian	103 (11.8)	52 (8.9)	22 (16.3)	27 (20.3)
Black	21 (2.4)	10 (1.7)	4 (3.0)	7 (5.3)
Weight (kg)				
Mean (SD)	88.3 9 (22.0)	86.8 (20.6)	90.3 (22.2)	91.3 (25.8)
>100kg, n (%)	231 (26.5)	149 (25.5)	37 (27.4)	37 (27.8)
≤100kg, n (%)	640 (73.5)	436 (74.5)	98 (72.6)	96 (72.2)
BMI, kg/m^2, mean (SD)	29.7 (7.0)	29.1 (6.4)	30.3 (7.2)	31.0 (8.6)
Duration of psoriasis, years, mean (SD)	16.8 (12.2)	16.7 (12.3)	18.2 (12.7)	15.6 (10.9)
Psoriatic arthritis, n (%)	128 (14.7)	77 (13.2)	28 (20.7)	21 (15.8)
% BSA involvement, mean (SD)	28.2 (16.8)	26.8 (15.6)	31.5 (19.8)	30.5 (17.9)

Study	NCT02203032 (NAVIGATE)			
	All patients	Nonrandomised	Patients randomised at Week 16	
Treatment	**Open-label ustekinumab run-in**	**Open-label ustekinumab continuation**	**Guselkumab**	**Ustekinumab**
IGA score (0–4), n (%)				
Mild, 2	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Moderate, 3	694 (79.7)	477 (81.5)	103 (76.3)	100 (75.2)
Severe, 4	176 (20.2)	108 (18.5)	32 (23.7)	33 (24.8)
PASI score, 0–72, mean (SD)	21.6 (9.2)	21.1 (9.2)	22.6 (9.3)	22.8 (9.4)
DLQI score (0–30), mean (SD)	14.5 (7.2)	14.2 (7.1)	15.5 (7.9)	14.4 (6.7)
PSSD score (0–100), n	866	584	133	132
Symptom score, mean (SD)	60.7 (20.4)	58.8 (20.1)	64.9 (20.3)	63.7 (20.8)
Sign score, mean (SD)	50.6 (24.7)	48.7 (24.0)	55.7 (25.5)	52.9 (25.6)
Prior treatments, n (%)				
Topical agents	834 (95.8)	562 (96.1)	128 (94.8)	126 (94.7)
Phototherapy	446 (51.3)	287 (49.1)	70 (51.9)	74 (55.6)
Conventional systemic agents	467 (53.6)	302 (51.6)	80 (59.3)	73 (54.9)
Anti-TNF agents (etanercept, infliximab, adalimumab)	125 (14.4)	63 (10.8)	32 (23.7)	26 (19.5)
Patients who had a contraindication, had an inadequate response, or were intolerant to ≥1 therapy	60 (48.0)	25 (39.7)	18 (56.3)	16 (61.5)

Key: BMI, body mass index; BSA, body surface area; CSR, clinical study report; DLQI, Dermatology Life Quality Index; IGA, Investigator Global Assessment; PASI, Psoriasis Symptom and Sign Diary; PSSD, Psoriasis Symptom and Sign Diary; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; SD, standard deviation; TNF, tumour necrosis factor.
Source: NAVIGATE CSR[59]

B.3.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The hypothesis and associated statistical analysis methods adopted for primary endpoint analyses in the VOYAGE 1, VOYAGE 2 and NAVIGATE trial programmes are tabulated in Appendix D.

All efficacy analyses were carried out based on the intent-to-treat (ITT) principle. The co-primary efficacy endpoints of VOYAGE 1 and VOYAGE 2 were powered to test for superiority of the guselkumab group with the placebo group. A comparison between adalimumab and placebo for the co-primary endpoints was also performed, as was a comparison between guselkumab and adalimumab which was tested for non-inferiority and superiority. The primary efficacy endpoint of NAVIGATE was powered to test for superiority of the guselkumab group with the ustekinumab group.

See Appendix D for the number of participants eligible to enter the trials and the CONSORT flow chart for patient disposition in VOYAGE 1, VOYAGE 2 and NAVIGATE.

B.3.5. Quality assessment of the relevant clinical effectiveness evidence

All three trials were conducted in accordance with good clinical practice (GCP) guidelines with a single protocol to promote consistency across sites, and with measures taken to minimise bias.

The accuracy and reliability of the clinical study data were assured by the selection of qualified investigators and an appropriate study centre, review of protocol procedures with the investigator and associated personnel before the study, and by periodic monitoring visits by the sponsor. In addition, an independent Data Monitoring Committee (DMC) was established with the responsibility of safeguarding the interests of study participants.

Randomisation in the trials was successfully carried out such that baseline characteristics of patients randomised were well balanced across treatment groups. There were few drop-outs in the trials, and patient withdrawals were accounted for with pre-defined, standard censoring methods. Patients and investigators remained blinded throughout the study, and all outcome assessments were conducted in accordance with trial validated methodology and were based on the ITT principle.

Quality assessment in accordance with the NICE-recommended checklist for RCT assessment of bias is presented in Appendix D. The risk of bias in all three trials is considered to be low.

B.3.6. Clinical effectiveness results of the relevant trials

Data are taken from primary publications[53, 54, 56] and supplemented with data from clinical study reports[57-59] and conference presentation.[55]

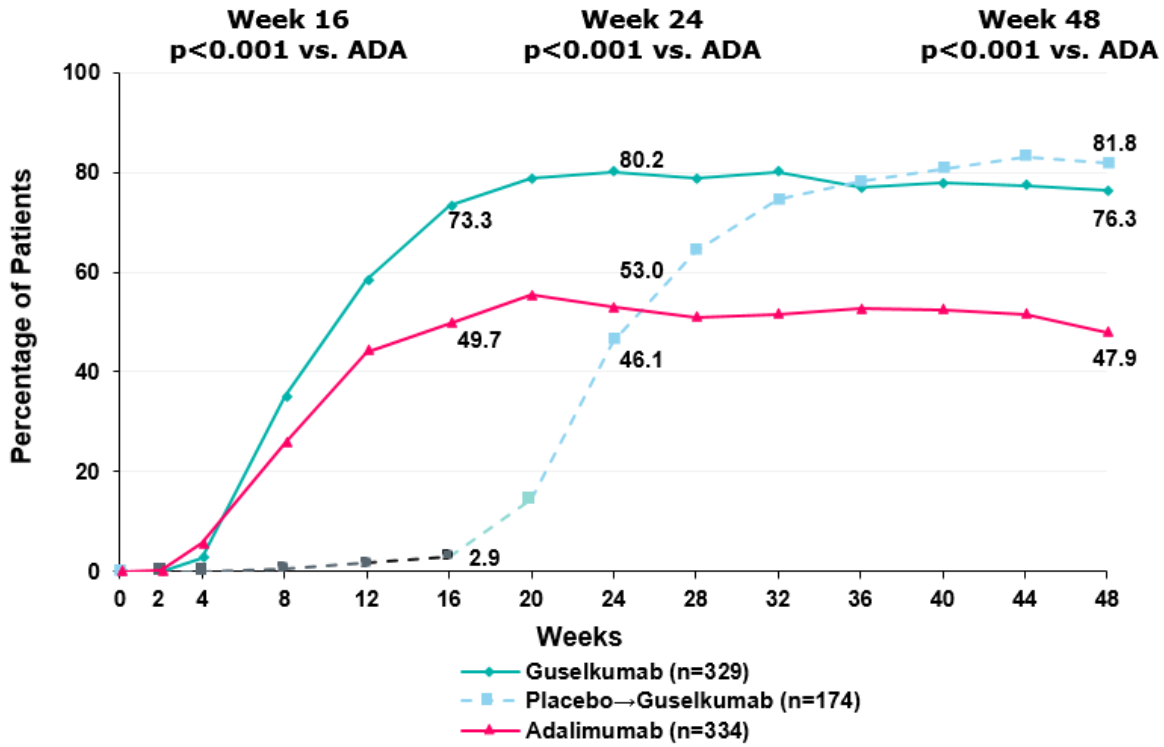
VOYAGE 1

Blinded treatment phase

Physician- and patient-reported outcomes at Weeks 16, 24 and 48 are summarised in Table 10. Guselkumab treatment was superior to placebo treatment for the co-primary endpoints ($p<0.001$) PASI 90 and IGA of 0/1.

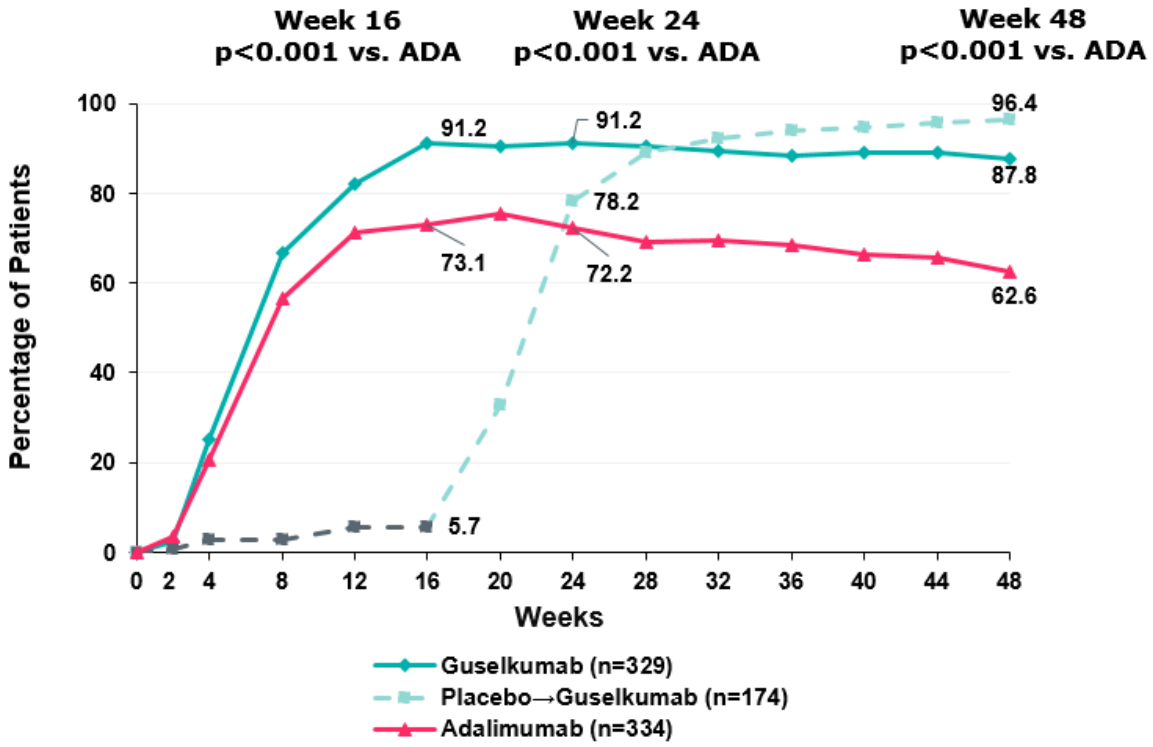
The effect of guselkumab on psoriasis was observed as early as the first post-baseline efficacy assessment (Week 2), and was sustained throughout the blinded treatment period (up to Week 48). As can be observed in Figure 5, a greater proportion of patients treated with guselkumab achieved a PASI 90 response compared to patients treated with placebo (70.4% more patients at Week 16) or adalimumab (28.4% more patients at Week 48). Similar observations were made when assessing PASI 75 response, as depicted in Figure 6.

Figure 5: Percent of patients randomised at Week 0 achieving PASI 90 response through Week 48 by visit



Key: ADA, adalimumab; PASI, Psoriasis Area and Severity Index.
Source: adapted from VOYAGE 1 CSR[57]

Figure 6: Percent of patients randomised at Week 0 achieving PASI 75 response through Week 48 by visit



Key: ADA, adalimumab; PASI, Psoriasis Area and Severity Index.
Source: adapted from VOYAGE 1 CSR[57]

When using the IGA tool to measure severity of disease, a significantly higher proportion of patients treated with guselkumab achieved total skin clearance (represented by an IGA score of 0) compared to patients treated with placebo (up to Week 16) and patients treated with adalimumab (up to Week 48) (Table 10; p<0.001). Nearly 25% more patients achieved total skin clearance with guselkumab compared to adalimumab.

Guselkumab showed superior clearance when used to treat regional psoriasis (such as scalp, finger nails and hand and foot) which is generally considered harder to treat. A significantly higher proportion of patients treated with guselkumab achieved absence of or very mild scalp psoriasis (represented by an ss-IGA score of 0/1), and clear or almost clear hand and foot psoriasis (represented by an hf-PGA score of

0/1) compared to patients treated with placebo (up to Week 16) and patients treated with adalimumab (up to Week 48) (Table 10).

Guselkumab had a comparable effect with adalimumab in the improvement of nail psoriasis severity (represented by the mean percent improvement in NAPSI score) but at Week 48, a significantly higher proportion of patients treated with guselkumab achieved clear or minimal fingernail disease (represented by an f-PGA score of 0/1) compared to patients treated with adalimumab (Table 10). Compared to placebo, guselkumab demonstrated a significant improvement in both nail psoriasis severity and the proportion of patients achieving clear or minimal fingernail disease at Week 16 (Table 10; $p<0.001$).

Patients treated with guselkumab reported a clinically meaningful improvement in their quality of life, with a higher proportion of patients achieving a minimally important difference in DLQI (≥5 points[60]) and PSSD signs/symptoms (≥40 points[61]) scores compared to patients treated with placebo (up to Week 16) (Table 10**;** [redacted]). Furthermore, a significantly higher proportion of patients treated with guselkumab reported no impact of disease on their quality of life, including daily activities, leisure, work and school and personal relationships (represented by a DLQI score of 0/1) and a significantly greater proportion of patients became symptom and sign free (represented by a PSSD score of 0) compared to patients treated with placebo (up to Week 16) and patients treated with adalimumab (up to Week 48) (Table 10; $p<0.001$).

These results show that guselkumab helps reduce the signs and symptoms of disease and is more likely to deliver sustained total skin clearance, improving the overall quality of life and reducing the psychosocial impact of psoriasis. This could lead to patients having greater confidence in engaging with family and friends and being less embarrassed and self-conscious due to their disease.

Table 10: Physician- and patient-reported outcomes in VOYAGE 1 at Weeks 16, 24, 48; randomised patients

	Week 16			Week 24		Week 48	
	Placebo	**Guselkumab**	**Adalimumab**	**Guselkumab**	**Adalimumab**	**Guselkumab**	**Adalimumab**
Physician reported outcomes							
IGA, n	174	329	334	329	334	329	334
IGA 0, n (%)	2 (1.1)	157 (47.7)[a]	88 (26.3)[a]	173 (52.6)[b]	98 (29.3)	166 (50.5)[b]	86 (25.7)
IGA 0/1, n (%)	12 (6.9)	280 (85.1)[ab]	220 (65.9)[a]	277 (84.2)[b]	206 (61.7)	265 (80.5)[b]	185 (55.4)
PASI, n	174	329	334	329	334	329	334
PASI 100, n (%)	1 (0.6)	123 (37.4)[ab]	57 (17.1)[a]	146 (44.4)[b]	83 (24.9)	156 (47.4)[b]	78 (23.4)
PASI 90, n (%)	5 (2.9)	241 (73.3)[ab]	166 (49.7)[a]	264 (80.2)[b]	177 (53.0)	251 (76.3)[b]	160 (47.9)
PASI 75, n (%)	10 (5.7)	300 (91.2)[ab]	244 (73.1)[a]	300 (91.2)[b]	241 (72.2)	289 (87.8)[b]	209 (62.6)
PASI 50, (%)	32 (18.4%)	315(95.7%)[a]	283 (84.7%)[a]	NR	NR	NR	NR
Baseline ss-IGA score ≥2, n	145	277	286	277	286	277	286
ss-IGA 0/1[d], n (%)	21 (14.5)	231 (83.4)[a]	201 (70.3)[a]	234 (84.5)[b]	198 (69.2)	217 (78.3)[b]	173 (60.5)
Baseline f-PGA score ≥2, n	88	174	173	174	173	174	173
f-PGA 0/1[d], n (%)	14 (15.9)	68 (39.1)[a]	88 (50.9)[a]	98 (56.3)	108 (62.4)	130 (74.7)[c]	107 (61.8)
NAPSI, n	99	194	191	194	191	194	191
% improvement in NAPSI, mean (SD)	-0.9 (57.9)	34.4 (42.5)[a]	38.0 (53.9)[a]	49.8 (44.2)	49.4 (60.0)	68.1 (43.0)	61.4 (49.2)
Baseline hf-PGA score ≥2, n	43	90	95	90	95	90	95
hf-PGA 0/1[d], n (%)	6 (14.0)	66 (73.3)[a]	53 (55.8)[a]	71 (78.9)[c]	54 (56.8)	68 (75.6)[c]	59 (62.1)
Patient-reported outcomes							
DLQI, n	170	322	328	322	328	322	328
Change in DLQI, mean (SD)	-0.6 (6.4)	-11.2 (7.2)[a]	-9.3 (7.8)[a]	-11.6 (7.6)	-9.5 (7.9)	-11.8 (7.9)	-9.2 (8.3)

	Week 16			Week 24		Week 48	
	Placebo	**Guselkumab**	**Adalimumab**	**Guselkumab**	**Adalimumab**	**Guselkumab**	**Adalimumab**
≥5 point improvement in DLQI, n (%)	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
DLQI score >1 at baseline, n	168	320	319	320	319	320	319
DLQI 0/1, n (%)	7 (4.2)	180 (56.3)[a]	123 (38.6)[a]	195 (60.9)[b]	126 (39.5)	200 (62.5)[b]	124 (38.9)
PSSD score, n	129	249	274	249	274	249	274
Change in symptom score, mean (SD)	-3.0 (19.6)	-41.9 (24.6)[a]	-35.4 (28.5)[a]	-44.0 (24.6)[b]	-36.0 (28.4)	-45.3 (25.5)[b]	-32.5 (31.1)
≥40 point improvement in symptom score, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in sign score, mean (SD)	-4.1 (17.9)	-44.6 (22.0)[a]	-39.7 (26.4)[a]	-47.2 (22.2)[b]	-40.1 (26.5)	-47.9 (23.1)[b]	-36.6 (29.3)
≥40 point improvement in sign score, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PSSD symptom score ≥1, n	129	248	273	248	273	248	273
Symptom score of 0, n (%)	1 (0.8)	67 (27.0)[a]	45 (16.5)[a]	90 (36.3)[b]	59 (21.6)	104 (41.9)[b]	63 (23.1)
Baseline PSSD sign score ≥1, n	129	248	274	248	274	248	274
Sign score of 0, n (%)	0 (0.0)	50 (20.2)[a]	32 (11.7)[a]	73 (29.4)[b]	40 (14.6)	89 (35.9)[b]	51 (18.6)

Key: DLQI, Dermatology Life Quality Index; f-PGA, The Physician's Global Assessment of Fingernail Psoriasis; hf-PGA, Physician's Global Assessment of Hands and/or Feet; IGA, Investigator Global Assessment; NAPSI, Nail Psoriasis Severity Index; NR, not recorded; PASI, Psoriasis Severity Index; PASI 50, 50% or greater improvement in PASI score from baseline; PASI 75, 75% or greater improvement in PASI score from baseline; PASI 90, 90% or greater improvement in PASI score from baseline; PASI 100, 100% improvement in PASI score from baseline; PSSD, Psoriasis symptoms and Signs Diary; SD, standard deviation; ss-IGA, scalp-specific Investigator Global Assessment.
Notes: Notes: [a], p <0.001 compared with placebo; [b], p <0.001 compared with adalimumab, [c], p <0.05 compared with adalimumab; [d], includes only patients also achieving ≥2-grade improvement in ss-IGA score and hf-PGA scores and ≥1-grade improvement in f-PGA score.
Sources: Blauvelt *et al*., 2017[53]; VOYAGE 1 CSR[57]

Open-label treatment period

Preliminary follow-up data from the long-term extension (LTE) phase (providing data for up to 2 years of guselkumab treatment) are summarised in Table 11. This phase of the study included patients randomised to guselkumab at Week 0, patients who crossed over from placebo to guselkumab at Week 16 and patients who crossed over from adalimumab to guselkumab at Week 52.

Data from this open-label treatment period demonstrate that guselkumab has the ability to sustain clinical benefits in patients through 2 years of continuous treatment, as demonstrated by patients randomised to guselkumab or who crossed over to guselkumab at Week 16 maintaining their improvements in physician-reported and patient-reported outcome assessments through Week 100 (Table 11).

In addition, patients treated with adalimumab who subsequently switched to guselkumab at Week 52 had improvements in both physician-reported and patient-reported outcomes from Week 52 to Week 100 (Table 11). This included a high proportion of patients achieving total skin clearance (represented by an IGA score of 0 or PASI100), over 27% more patients achieve PASI 100 or IGA 0 when they are switched from adalimumab to guselkumab. Furthermore, 35% more patients report no impact of disease on their quality of life (represented by a DLQI score of 0/1) and over 10% more patients being symptom and sign free (represented by a PSSD score of 0) when they were switched to guselkumab.

Maintenance of PASI 90 and PASI 75 response with guselkumab treatment can be clearly observed in

Figure 7 and Figure 8.

Figure 7: Percent of patients randomised at Week 0 achieving PASI 90 response through Week 100 by visit

Figure 8: Percent of patients randomised at Week 0 achieving PASI 75 response through Week 100 by visit

Table 11: Clinical efficacy assessments from the long term extension studies of VOYAGE 1

	Placebo to guselkumab		Guselkumab		Adalimumab to guselkumab	
	Week 52	**Week 100**	**Week 52**	**Week 100**	**Week 52**	**Week 100**
Physician reported outcomes						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean % PASI improvement (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IGA 0/1, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IGA 0, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient-reported outcomes						
	Placebo to guselkumab		**Guselkumab**		**Adalimumab to guselkumab**	
	Week 48	**Week 100**	**Week 48**	**Week 100**	**Week 48**	**Week 100**
Baseline PSSD symptom score >0, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptom score of 0, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PSSD sign score >0, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sign score of 0, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI score >1 at baseline, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI 0/1, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: DLQI, Dermatology Life Quality Index; IGA, Investigator Global Assessment; PASI, Psoriasis Severity Index; PASI 75, 75% or greater improvement in PASI score from baseline; PASI 90, 90% or greater improvement in PASI score from baseline; PASI 100, 100% improvement in PASI score from baseline; PSSD, Psoriasis symptoms and Signs Diary; SD, standard deviation.
Source: Griffiths *et al*. 2017[55]

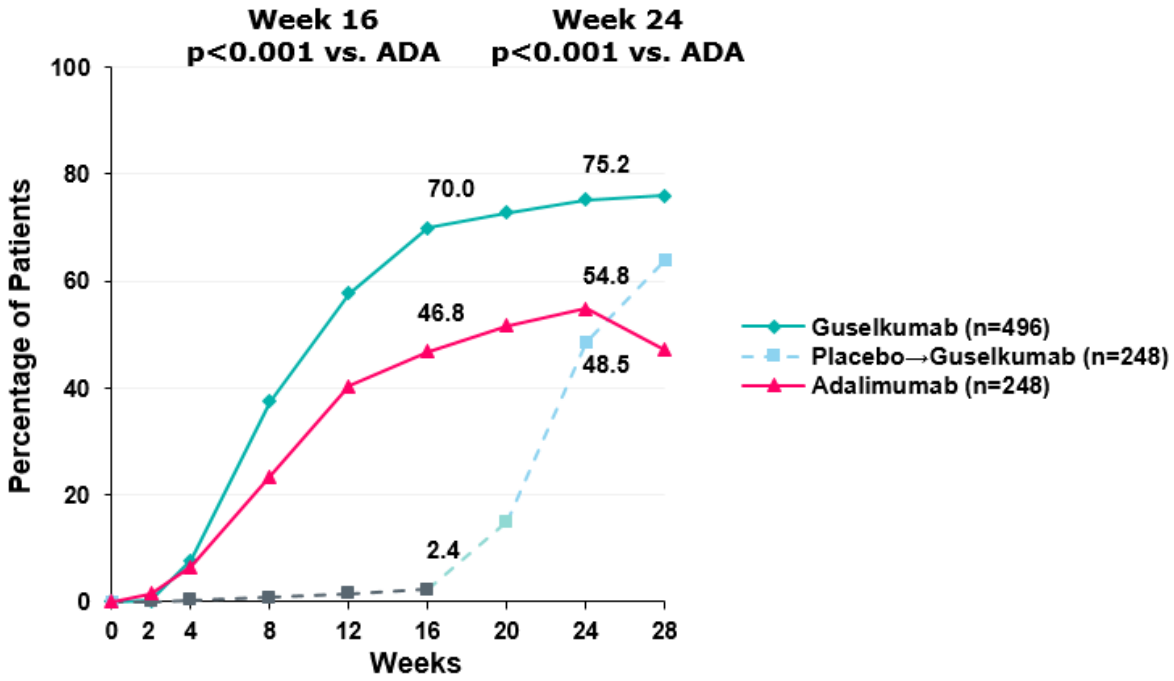
VOYAGE 2

Active comparator-controlled period

Physician and patient-reported outcomes at Weeks 16 and 24 are summarised in Table 12. Guselkumab treatment was significantly superior to placebo treatment for the co-primary endpoints (p<0.001) PASI 90 and IGA score of 0/1.

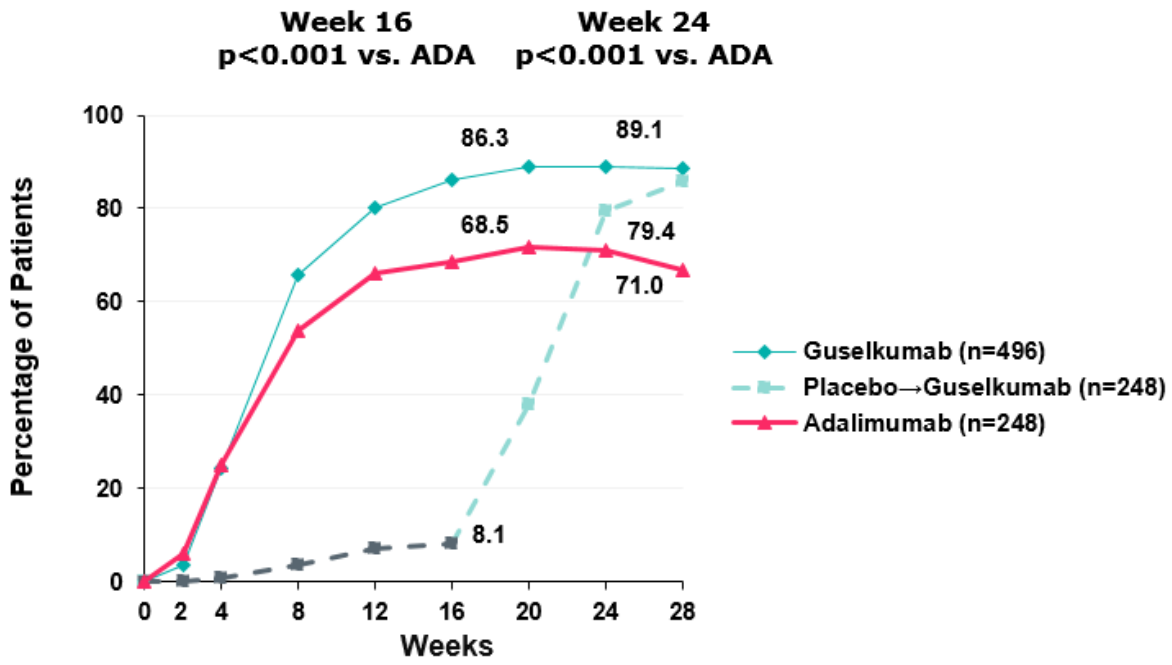
The effect of guselkumab on psoriasis was observed as early as the first post-baseline efficacy assessment (Week 2), and was sustained throughout the active comparator-controlled period (up to Week 24). As can be observed in Figure 9, a greater proportion of patients treated with guselkumab achieved and sustained a PASI 90 response compared to patients treated with placebo (up to Week 16) or adalimumab (up to Week 24). Similar observations were made when assessing PASI 75 response in the active treatment arms, as depicted in Figure 10.

Figure 9: Percent of patients randomised at Week 0 achieving PASI 90 response through Week 28 by visit



Key: ADA, adalimumab; PASI, Psoriasis Area and Severity Index.
Source: Adapted from VOYAGE 2 CSR[58]

Figure 10: Percent of patients randomised at Week 0 achieving PASI 75 response through Week 24 by visit



Key: ADA, adalimumab; PASI, Psoriasis Area and Severity Index.
Source: Adapted from VOYAGE 2 CSR[58]

When using the IGA tool to measure severity of disease, a significantly higher proportion of patients treated with guselkumab achieved total skin clearance (represented by an IGA score of 0) compared to patients treated with placebo (at Week 16) and patients treated with adalimumab (at Week 24) (Table 12; p<0.001). Nearly 20% more patients achieved total skin clearance with guselkumab compared to adalimumab.

Guselkumab showed superior clearance when used to treat regional psoriasis (such as scalp, finger nails and hand and foot) which is generally considered harder to treat. A significantly higher proportion of patients treated with guselkumab similarly achieved absence of or very mild scalp psoriasis (represented by an ss-IGA score of 0/1), and clear or almost clear hand and foot psoriasis (represented by an hf-PGA score of 0/1) compared to patients treated with placebo (up to Week 16) and patients treated with adalimumab (up to Week 24) (Table 12).

Guselkumab had a comparable effect to adalimumab in the improvement of nail/fingernail psoriasis, but demonstrated a significant improvement in both nail psoriasis severity (represented by the mean percent improvement in NAPSI score) and the proportion of patients achieving clear or minimal fingernail disease (represented by an f-PGA score of 0/1) compared to placebo (up to Week 16) (Table 12; $p<0.001$).

Patients treated with guselkumab reported a clinically meaningful improvement in their quality of life, with a higher proportion of patients achieving a minimally important difference in DLQI (≥5 points[60]) and PSSD signs/symptoms (≥40 points[61]) scores compared to patients treated with placebo (up to Week 16) (Table 12; [redacted]). Furthermore, a significantly higher proportion of patients treated with guselkumab reported no impact of disease on their quality of life, including daily activities, leisure, work and school and personal relationships (represented by a DLQI score of 0/1); and a significantly greater proportion of patients became symptom and sign free (represented by a PSSD score of 0) compared to patients treated with placebo (up to Week 16) and patients treated with adalimumab (up to Week 24) (Table 12).

As observed in SF-36 data, patients treated with guselkumab also experienced significant improvements in their ability to perform physical and cognitive tasks (as represented by improvements from baseline in the physical component score [PCS] and mental component score [MCS]) compared to placebo at Week 16 (Table 12; $p<0.001$). Patients also experienced significant improvements in their ability to perform occupational tasks (measured by the WLQ), and anxiety and depression was significantly reduced with guselkumab treatment with approximately 60% of patients with either depression or anxiety at baseline reporting no depression or anxiety (represented by a HADS score of <8) after 24 weeks of guselkumab treatment (Table 12).

As observed in VOYAGE 1, these results show that guselkumab helps reduce the signs and symptoms of disease and is more likely to deliver sustained total skin clearance, improving the overall quality of life and reducing the psychosocial impact of psoriasis.

Table 12: Physician- and patient-reported outcomes in VOYAGE 2 at Weeks 16 and 24; randomised patients

	Week 16			Week 24	
	Placebo	**Guselkumab**	**Adalimumab**	**Guselkumab**	**Adalimumab**
Physician reported outcomes					
IGA, n	248	496	248	496	248
IGA 0, n (%)	2 (0.8)	215 (43.3)[b]	71 (28.6)[a]	257 (51.8)[b]	78 (31.5)
IGA 0/1, n (%)	21 (8.5)	417 (84.1)[ab]	168 (67.7)[a]	414 (83.5)[b]	161 (64.9)
PASI, n	248	496	248	496	248
PASI 100, n (%)	2 (0.8)	169 (34.1)[ab]	51 (20.6)[a]	219 (44.2)[b]	66 (26.6)
PASI 90, n (%)	6 (2.4)	347 (70.0)[ab]	116 (46.8)[a]	373 (75.2)[b]	136 (54.8)
PASI 75, n (%)	20 (8.1)	428 (86.3)[ab]	170 (68.5)[a]	442 (89.1)[b]	176 (71.0)
PASI 50, (%)	53 (21.4%)	467 (94.2%)[a]	210 (84.7%)[a]	NR	NR
Baseline ss-IGA score ≥2, n	202	408	194	408	194
ss-IGA 0/1[d], n (%)	22 (10.9)	329 (80.6)[a]	130 (67.0)[a]	348 (85.3)[b]	131 (67.5)
Baseline f-PGA score ≥2, n	123	246	124	246	124
f-PGA 0/1[d], n (%)	18 (14.6)	128 (52.0)[a]	74 (59.7)[a]	154 (62.6)	83 (66.9)
NAPSI, n	140	280	140	280	140
% improvement in NAPSI, mean (SD)	1.8 (53.8)	39.6 (45.6)[a]	46.9 (48.1)[a]	55.0 (46.8)	53.7 (49.5)
Baseline hf-PGA score ≥2, n	63	114	56	114	56
hf-PGA 0/1[d], n (%)	9 (14.3)	88 (77.2)[a]	40 (71.4)[a]	93 (81.6)[b]	37 (66.1)
Patient-reported outcomes					
SF-36, n	248	494	246	494	246
PCS score, mean (SD)	0.94 (6.6)	5.46 (7.8)[a]	3.92 (6.6)[a]	5.60 (8.1)	3.65 (7.2)
PCS score, median	0.75	4.26	3.10	4.44	3.20
MCS score, mean (SD)	0.57 (8.8)	5.66 (9.5)[a]	4.57 (9.4)[a]	5.96 (10.2)	4.16 (10.3)

	Week 16			Week 24	
	Placebo	**Guselkumab**	**Adalimumab**	**Guselkumab**	**Adalimumab**
MCS score, median	0.57	3.90	3.25	4.44	3.31
DLQI, n	248	494	249	495	247
Change in DLQI, mean (SD)	-2.6 (6.9)	-11.3 (6.8)[a]	-9.7 (6.8)[a]	-11.9 (7.0)	-9.9 (7.4)
≥5 point improvement in DLQI, n (%)	[redacted]	[redacted]	[redacted]	NR	NR
DLQI score >1 at baseline, n	246	491	246	491	246
DLQI 0/1, n (%)	8 (3.3)	254 (51.7)[a]	96 (39.0)[a]	283 (57.6)[b]	101 (41.1)
PSSD score, n	198	411	201	411	201
Change in symptom score, mean (SD)	-8.3 (23.7)	-40.4 (26.5)[a]	-32.8 (24.9)[a]	-42.1 (26.8)[b]	-31.9 (27.0)
≥40 point improvement in symptom score, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in sign score, mean (SD)	-9.8 (22.8)	-42.9 (23.7)[a]	-34.6 (23.5)[a]	-44.5 (24.1)[b]	-33.6 (25.3)
≥40 point improvement in sign score, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PSSD symptom score ≥1, n	198	410	200	410	200
Symptom score of 0, n (%)	0 (0.0)	112 (27.3)[a]	30 (15.0)[a]	144 (35.1)[c]	45 (22.5)
Baseline PSSD sign score ≥1, n	198	411	201	411	201
Sign score of 0, n (%)	0 (0.0)	86 (20.9)	21 (10.4)[a]	114 (27.7)	34 (16.9)
HADS, n	248	496	248	495	246
Mean improvement in hospital anxiety score, mean (SD)	-0.2 (2.93)	-1.7 (3.43)[a]	-1.1 (3.44)[a]	-2.0 (3.57)	-1.0 (3.57)
Mean improvement in depression score, mean (SD)	-0.1 (2.93)	-1.6 (3.63)[a]	-1.2 (3.36)[a]	-1.7 (3.79)	-1.1 (3.48)

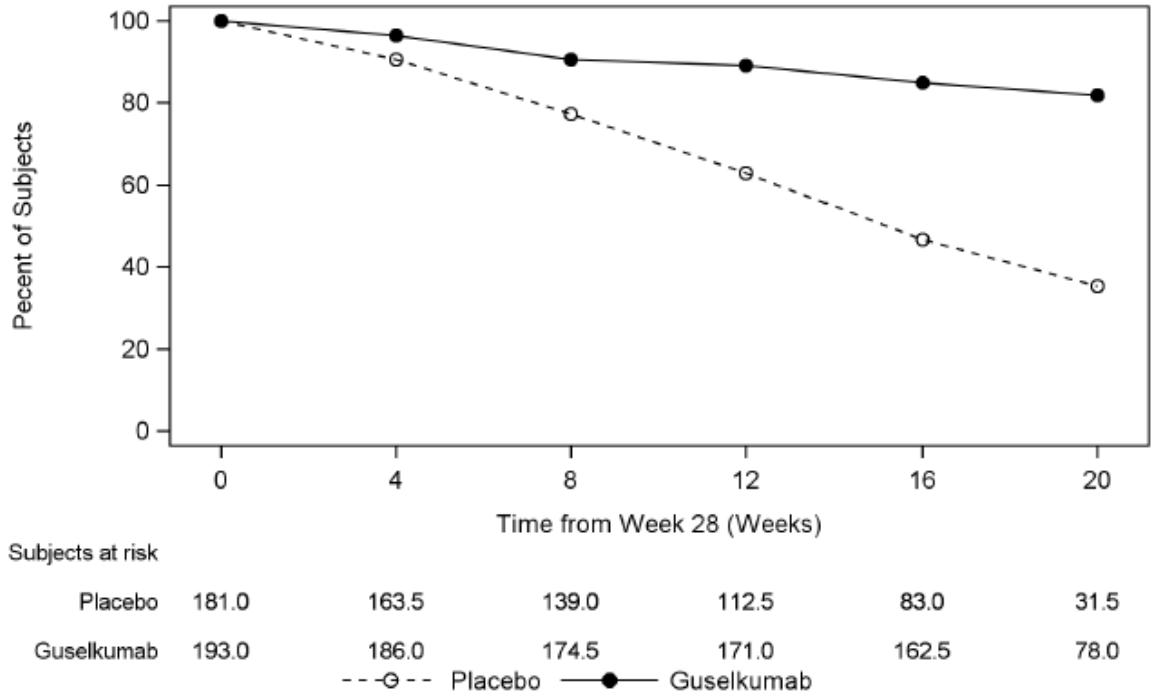
	Week 16			Week 24	
	Placebo	**Guselkumab**	**Adalimumab**	**Guselkumab**	**Adalimumab**
Patients with anxiety at baseline achieving HADs score <8, n/N (%)	21/81 (25.9)	95/185 (51.4)	44/98 (44.9)	108/185 (58.4)[c]	42/98 (42.9)
Patients with depression at baseline achieving HADs score <8, n/N (%)	19/66 (28.8)	77/134 (57.5)	39/74 (52.7)	76/127 (59.8)	32/69 (46.4)
WLQ, n	248	496	248	495	246
Physical Demands score, mean (SD)	0.4 (15.16)	-7.5 (19.06)[a]	-2.9 (16.01)	-6.9 (19.71)	-3.3 (17.77)
Time Management score, mean (SD)	0.1 (19.30)	-6.0 (19.36)[a]	-7.5 (20.21)[a]	-7.5 (19.66)	-7.6 (21.47)
Mental - Interpersonal score, mean (SD)	-0.7 (14.37)	-5.3 (16.21)[a]	-3.7 (13.83)	-6.3 (17.60)	-3.2 (16.63)
Output Demands score, mean (SD)	-2.2 (12.68)	-5.8 (18.41)[a]	-3.3 (17.19)	-6.2 (20.02)	-2.2 (20.45)

Key: CSR, clinical study review; DLQI, Dermatology Life Quality Index; f-PGA, The Physician's Global Assessment of Fingernail Psoriasis; HADS, Hospital Anxiety and Depression Scores; hf-PGA, Physician's Global Assessment of Hands and/or Feet; IGA, Investigator Global Assessment; NAPSI, Nail Psoriasis Severity Index; NR, not recorded; PASI, Psoriasis Severity Index; PASI 50, 50% or greater improvement in PASI score from baseline; PASI 75, 75% or greater improvement in PASI score from baseline; PASI 90, 90% or greater improvement in PASI score from baseline; PASI 100, 100% improvement in PASI score from baseline; PSSD, Psoriasis symptoms and Signs Diary; SD, standard deviation; ss-IGA, scalp-specific Investigator Global Assessment; WLQ, Work Limitations Questionnaire.
Notes: [a], p <0.001 compared with placebo; [b], p <0.001 compared with adalimumab, [c], p <0.05 compared with adalimumab; [d], includes only patients also achieving ≥2-grade improvement in ss-IGA score and hf-PGA scores and ≥1-grade improvement in f-PGA score.
Sources: Reich *et al*., 2017[54]; VOYAGE 2 CSR[58]

Randomised withdrawal/retreatment period

Continuation of guselkumab therapy resulted in a significantly better maintenance of response than withdrawal, as patients continuing to receive guselkumab maintained a PASI 90 response through Week 48 whereas patients withdrawing from guselkumab treatment began to lose response 4 weeks after being withdrawn from treatment, as depicted in Figure 11.

Figure 11: Life-table estimate of percent of patients randomised at Week 28 maintaining PASI 90 response



Key: PASI, Psoriasis Area and Severity Index.
Source: VOYAGE 2 CSR[58]

The proportion of patients who maintained their PASI 90 response through Week 48 was significantly greater in the maintenance group compared to the withdrawal group (81.8% versus 35.4%; p<0.001). The median time to loss of PASI 90 response was 15.2 weeks for patients in the withdrawal group; however, this could not be estimated for the maintenance group since more than 50% of maintenance patients remained PASI 90 responders at Week 48.

A significantly greater proportion of patients in the maintenance group achieved a PASI 90 response at Week 48 compared to patients who were withdrawn from guselkumab (88.6% versus 36.8%; p<0.001). These results are consistent with the major secondary endpoint using life-table estimates for maintenance of PASI 90 (Figure 11). Furthermore, a significantly greater proportion of patients receiving continuous guselkumab maintenance therapy achieved total skin clearance or minimal psoriasis (represented by an IGA score of 0/1) at Week 48 compared to patients in the withdrawal group (90.2% and 45.1%; p<0.001).

Effect of guselkumab in adalimumab non-responders

Patients with an inadequate response to adalimumab (PASI 90 non-responders at Week 28) achieved treatment effect upon switching to guselkumab that resulted in substantial improvements in PASI response, IGA scores and HRQL scores. This indicates that patients with a primary non-response to anti TNF may respond to the different mode of action of guselkumab.

The proportion of patients with a PASI 90 response increased within 4 weeks of the first guselkumab 100mg dose and was 66.1% by Week 48, which was comparable with the proportion of PASI 90 responders in the placebo to guselkumab group at Week 48 (60.0%).

The proportion of patients achieving total skin clearance or minimal psoriasis (represented by an IGA score of 0/1) at Week 48 was 81.3% in the adalimumab non-responders group who switched to guselkumab, comparable with that of the placebo to guselkumab group at the same timepoint (80.0%).

The median change from baseline in DLQI score represented clinically meaningful improvements in disease specific quality of life at both Week 28 (-5.0) and Week 48 (-11.0). Substantial improvements in PSSD scores were also observed in the adalimumab non-responders who switched to guselkumab treatment.

NAVIGATE

Primary and major secondary endpoints for the active treatment phase (Week 28 through Week 40) are summarised in Table 13. Guselkumab treatment was statistically significantly superior to ustekinumab treatment for the primary endpoint,

(p<0.001), this indicates that patient that have a primary failure to ustekinumab do response to the different mode of action of guselkumab.

Patients with an inadequate response to ustekinumab (IGA score ≥2 at Week 16) achieved treatment effect upon switching to guselkumab that resulted in substantial improvements in PASI response and IGA scores. The number of visits at which patients achieved total skin clearance and/or minimal psoriasis (represented by an IGA score of 0 and 0/1) and/or a PASI 90 response was significantly higher in patients treated with guselkumab compared to ustekinumab (from Week 28 through Week 40) (Table 13; p<0.001).

The proportion of patients with a PASI 90 response at three or four visits, and the proportion of patients with total skin clearance (represented by an IGA score of 0) at three of four visits was also higher in the guselkumab group compared to the ustekinumab group (54.1% versus 23.3% and 16.3% versus 8.3%, respectively).

Table 13: Key efficacy endpoints for NAVIGATE

		Guselkumab	Ustekinumab
Randomised patients		135	133
Primary endpoint	Number of visits with an IGA score of 0/1 and ≥2-grade improvement week 28-40		
	Mean (SD)	1.5 (1.6)[a]	0.7 (1.3)
	Median (range)	1.0 (0-4)	0.7 (0-4)
	0 visits, n (%)	56 (41.5)	96 (72.2)
	1 visits, n (%)	21 (15.6)	11 (8.3)
	2 visits, n (%)	14 (10.4)	7 (5.3)
	3 visits, n (%)	20 (14.8)	10 (7.5)
	4 visits, n (%)	24 (17.8)	9 (6.8)
Major secondary endpoints	Number of visits with a PASI 90 response week 28-40		
	Mean (SD)	2.2 (1.7)[a]	1.1 (1.5)
	Median	3.0 (0-4)	0.0 (0-4)
	0, n (%)	39 (28.9)	76 (57.1)
	1, n (%)	15 (11.1)	19 (14.3)
	2, n (%)	8 (5.9)	7 (5.3)
	3, n (%)	24 (17.8)	10 (7.5)
	4, n (%)	49 (36.3)	21 (15.8)
	Number of visits with an IGA response of 0 week 28-40		
	Mean (SD)	0.9 (1.3)[a]	0.4 (1.1)

		Guselkumab	Ustekinumab
	Median (range)	0.0 (0-4)	0.0 (0-4)
	0, n (%)	79 (58.5)	115 (86.5)
	1, n (%)	19 (14.1)	3 (2.3)
	2, n (%)	15 (11.1)	4 (3.0)
	3, n (%)	10 (7.4)	4 (3.0)
	4, n (%)	12 (8.9)	7 (5.3)
	IGA of 0/1 and ≥2-grade improvement from Week 16, n (%)	42 (31.1)[a]	19 (14.3)

Key: CSR, Clinical Study Report; IGA, Investigator Global Assessment; PASI, Psoriasis Severity Index; PASI 90, 90% or greater improvement in PASI score from baseline; SD, standard deviation.
Notes: [a], p <0.001 compared with ustekinumab
Source: NAVIGATE CSR[59]

B.3.7. Subgroup analysis

In pre-specified subgroup analyses of the VOYAGE and NAVIGATE trials, a consistent benefit in favour of guselkumab was observed, as summarised in Appendix E. These groups included patients who had previously received phototherapy, systemic non-biological therapy and systemic biological therapy versus those who had not, and varying severity of disease as assessed through baseline PASI, IGA, involved BSA and DLQI scores.

B.3.8. Meta-analysis

Meta-analyses across all of the guselkumab trials are not considered appropriate due to the differences in study design and objective across the VOYAGE and NAVIGATE trials. Pairwise meta-analyses of PASI 90 and PASI 75 response across the VOYAGE trials are provided in Appendix D, and show low heterogeneity with an I^2 of ≤10% (0% for PASI 90 response and PASI 75 response for guselkumab versus adalimumab). This supports the consistency of outcomes in the VOYAGE trials (see Section B.3.6).

B.3.9. Indirect and mixed treatment comparisons

Methods

A series of NMAs were performed using a Bayesian framework with a model for dichotomous outcomes deriving comparisons between interventions for the outcomes of interest, including efficacy (PASI 90, PASI 75, PASI 50, PASI 100, PGA/IGA), safety (AE, SAE, WDAE) and HRQL (DLQI) outcomes, at the end of treatment induction (12-16 weeks of treatment). A conventional NMA was not feasible for treatment maintenance as study designs allow crossover to active treatment from the placebo groups after the induction period (see Appendix D). Novel methods that could facilitate indirect comparisons across treatment maintenance are currently under investigation.[62]

Fixed effects and random effects models were fitted and run using both an unadjusted relative effects analysis, as well as incorporating a meta-regression adjustment to account for variations in several covariates. This included adjustment for the placebo response rate, differences between which are reflective of differences in the baseline risk of trial populations. A risk-difference NMA was also conducted as a simpler approach to accounting for cross-trial heterogeneity represented by differences in placebo response rates. These approaches are in line with NICE technical support documents on evidence synthesis.[63-65]

Relative effects are reported as risk ratios (RR) and associated 95% credible intervals (CrI); risk differences (RD) are reported as such with associated 95% CrI. Surface Under the Cumulative Ranking curves (SUCRA) are presented as a means to reflect treatment ranking[66] and Bayesian probability values of achieving a response with one intervention versus another are reported for comparisons involving guselkumab 100mg (p[guselkumab better]).

The synthesised evidence network used in base case analyses was broader than the decision comparator set relevant to this submission, as it was designed for use in multiple countries globally (see Appendix D). A sensitivity analysis was conducted to focus the synthesised evidence network to the decision problem. Full details of the methodology for the NMAs and all evidence networks and outcomes are provided in Appendix D.

Results

Key efficacy and safety results are presented in the following sections, and are focused to comparisons of guselkumab and alternative biologic treatments available in the NHS.

All results presented are taken from random effects models that better fit the data than the fixed effects models. Baseline risk-adjusted model outcomes are presented for relative effects analyses, as this model tended to fit the data better for most endpoints (including the primary trial endpoint of PASI 90) based on criteria outlined by NICE[64] and determined *a priori*.

Model fit statistics are provided in Appendix D along with further outcomes of the NMAs (including data for all treatments included in the network and alternatively adjusted relative effect models).

Relative effects analyses

A summary of baseline risk-adjusted model outcomes for relative effects analyses is provided in Table 14.

As can be seen from this summary, the consistent outcome for guselkumab was one of comparable or greater clinical efficacy and generally similar tolerability versus alternative biologics used in current practice. Values greater than 1 are in favour of guselkumab and are considered significant when CrI do not span unity; these differences are shaded grey in Table 14

Full league tables of key endpoints of interest to this submission (PASI 90 response, PASI 75 response, AE rates) are presented in the following sub-sections; full league tables of additional endpoints are presented in Appendix D.

Table 14: Summary of pairwise comparisons with guselkumab from baseline risk-adjusted relative effects analyses

	Values >1 favour guselkumab 100mg						Values <1 favour guselkumab 100mg		
	PASI 90	**PASI 75**	**IGA/PGA 0/1**	**PASI 100**	**PASI 50**	**DLQI 0/1**	**AE**	**SAE**	**WDAE**
Placebo	43.22 (39.06, 46.88)	16.37 (15.74, 16.92)	16.88 (15.86, 17.80)	63.33 (54.63, 72.31)	6.23 (6.06, 6.35)	8.63 (7.62, 9.60)	1.05 (0.96, 1.15)	1.05 (0.58, 1.82)	0.99 (0.49, 2.02)
Ixekizumab 80mg Q2W	1.00 (0.88, 1.12)	0.98 (0.93, 1.02)	0.96 (0.90, 1.04)	0.90 (0.74, 1.08)	-	0.87 (0.75, 1.00)	0.89 (0.80, 1.00)	1.20 (0.59, 2.40)	0.64 (0.27, 1.45)
Secukinumab 300mg	1.20 (1.04, 1.37)	1.07 (1.01, 1.13)	1.02 (0.94, 1.12)	1.23 (1.00, 1.49)	1.02 (0.97, 1.07)	0.95 (0.82, 1.09)	0.91 (0.81, 1.04)	1.01 (0.49, 2.16)	1.40 (0.55, 3.54)
Secukinumab 150mg	1.64 (1.39, 1.96)	1.21 (1.13, 1.30)	1.25 (1.13, 1.45)	2.29 (1.78, 2.92)	1.08 (1.01, 1.17)	1.13 (0.95, 1.32)	0.89 (0.79, 1.00)	0.96 (0.44, 2.21)	1.53 (0.56, 4.16)
Ustekinumab 90mg	1.52 (1.29, 1.80)	1.20 (1.12, 1.29)	1.18 (1.08, 1.30)	2.97 (2.12, 4.16)	1.05 (1.01, 1.10)	0.99 (0.84, 1.16)	1.04 (0.92, 1.19)	1.25 (0.58, 2.94)	1.15 (0.36, 2.90)
Ustekinumab 45/90mg	1.63 (1.37, 1.95)	1.30 (1.21, 1.41)	1.30 (1.17, 1.50)	1.83 (1.47, 2.28)	-	1.21 (1.03, 1.41)	0.95 (0.84, 1.07)	1.42 (0.65, 3.05)	1.46 (0.52, 4.55)
Ustekinumab 45mg	1.57 (1.34, 1.84)	1.27 (1.18, 1.37)	1.26 (1.15, 1.39)	2.00 (1.54, 2.60)	1.09 (1.04, 1.13)	1.01 (0.86, 1.20)	0.99 (0.87, 1.11)	1.46 (0.66, 3.20)	2.51 (0.98, 6.94)
Infliximab 5mg/kg	1.30 (1.09, 1.55)	1.06 (0.99, 1.14)	0.95 (0.88, 1.04)	1.78 (0.36, 45.11)	1.01 (0.96, 1.05)	-	0.81 (0.72, 0.93)	0.51 (0.26, 1.03)	0.38 (0.16, 0.95)
Adalimumab 40mg	1.48 (1.31, 1.67)	1.24 (1.18, 1.32)	1.29 (1.19, 1.40)	1.97 (1.62, 2.37)	1.13 (1.08, 1.18)	1.50 (1.30, 1.74)	0.96 (0.88, 1.06)	1.00 (0.52, 1.91)	0.97 (0.44, 2.05)
Etanercept 50mg BIW	3.07 (2.62, 3.58)	1.72 (1.60, 1.85)	1.76 (1.60, 1.96)	5.89 (4.47, 7.76)	1.21 (1.14, 1.27)	1.49 (1.26, 1.73)	0.95 (0.85, 1.06)	1.20 (0.61, 2.22)	0.83 (0.37, 1.82)
Etanercept 50mg QW	5.36 (3.73, 7.98)	2.40 (1.95, 2.98)	2.67 (2.07, 3.50)	10.02 (2.36, 49.29)	1.38 (1.24, 1.58)	2.09 (1.51, 3.02)	1.08 (0.88, 1.33)	0.73 (0.29, 1.93)	1.13 (0.38, 4.04)
Etanercept 25mg BIW	6.01 (4.14, 9.03)	2.41 (2.00, 2.97)	2.42 (1.97, 3.06)	-	1.45 (1.31, 1.65)	-	-	-	0.95 (0.23, 5.05)

Key: AE, adverse event; BIW, biweekly; DLQI, Dermatology Life Quality Index; IGA/PGA, Investigator's Global Assessment/Physician's Global Assessment; PASI, Psoriasis Area Severity Index; SAE, serious adverse event; WDAE, withdrawal due to adverse event; QW, once weekly.

PASI 90 response

A league table summary of RR and p[guselkumab better] outcomes from the baseline risk-adjusted NMA for PASI 90 response is provided as Figure 12.

As observed in Figure 12, guselkumab demonstrates comparable or greater efficacy compared with alternative biologics at the end of induction. Specifically, guselkumab efficacy is similar to or greater than the IL-17 class of biologic treatment (RR versus ixekizumab = 1.00 [95% CrI: 0.88, 1.12]; p[guselkumab better] = 50%; RR versus secukinumab = 1.20 [95% CrI: 1.04, 1.37]; p[guselkumab better] = 99%) and greater than the anti-TNF (RR versus adalimumab = 1.48 [95% CrI: 1.31, 1.67]; p[guselkumab better] = 100%) and IL-12/23 classes (RR versus ustekinumab = 1.52-1.63 [95% CrI: 1.29, 1.95]; p[guselkumab better] = 100%).

A sensitivity analysis that focused the evidence network to the decision comparator set corroborated the base case network analyses presented above (Figure 12). As observed in Figure 13, RR outcomes from this focused network (focused to the decision problem) were consistent with those previously reported (RR versus ixekizumab = 1.00 [95% CrI: 0.87, 1.12]; RR versus secukinumab = 1.09 [95% CrI: 0.91, 1.31]; RR versus adalimumab = 1.46 [95% CrI: 1.28, 1.67]; RR versus ustekinumab = 1.54-1.64 [95% CrI: 1.29, 2.00]).

Figure 12: League table summary of relative risks and p[guselkumab better] for the PASI 90 response at the end of induction analyses; baseline risk-adjusted

49.84 Ixekizumab 80 mg Q2W												
1.001 (0.89 – 1.13)	**NA** Guselkumab 100 mg											
1.2 (1.07 – 1.35)	1.2 (1.04 – 1.37)	**99.43** Secukinumab 300 mg										
1.3 (1.11 – 1.52)	1.3 (1.09 – 1.55)	1.08 (0.92 – 1.28)	**99.70** Infliximab 5 mg/kg									
1.48 (1.29 – 1.69)	1.48 (1.31 – 1.67)	1.23 (1.06 – 1.43)	1.14 (0.94 – 1.38)	**100.00** Adalimumab 40 mg								
1.52 (1.31 – 1.78)	1.52 (1.29 – 1.80)	1.27 (1.08 – 1.50)	1.17 (0.97 – 1.42)	1.03 (0.86 – 1.23)	**100.00** Ustekinumab 90 mg							
1.57 (1.37 – 1.81)	1.57 (1.34 – 1.84)	1.31 (1.13 – 1.53)	1.21 (1.01 – 1.46)	1.06 (0.90 – 1.26)	1.03 (0.89 – 1.19)	**100.00** Ustekinumab 45 mg						
1.63 (1.41 – 1.91)	1.63 (1.37 – 1.95)	1.36 (1.17 – 1.60)	1.26 (1.03 – 1.54)	1.1 (0.92 – 1.33)	1.07 (0.88 – 1.31)	1.04 (0.86 – 1.26)	**100.00** Ustekinumab 45/90 mg					
1.65 (1.42 – 1.94)	1.65 (1.38 – 1.97)	1.38 (1.21 – 1.58)	1.27 (1.05 – 1.55)	1.12 (0.93 – 1.35)	1.09 (0.89 – 1.32)	1.05 (0.87 – 1.27)	1.01 (0.83 – 1.23)	**100.00** Secukinumab 150 mg				
3.07 (2.71 – 3.49)	3.07 (2.62 – 3.58)	2.56 (2.22 – 2.96)	2.37 (1.98 – 2.81)	2.08 (1.75 – 2.46)	2.02 (1.71 – 2.38)	1.95 (1.66 – 2.29)	1.89 (1.56 – 2.26)	1.86 (1.55 – 2.21)	**100.00** Etanercept 50 mg BIW			
5.37 (3.77 – 7.95)	5.36 (3.73 – 7.98)	4.48 (3.12 – 6.67)	4.14 (2.84 – 6.25)	3.63 (2.51 – 5.44)	3.53 (2.42 – 5.32)	3.42 (2.36 – 5.12)	3.3 (2.25 – 4.98)	3.25 (2.22 – 4.91)	1.75 (1.22 – 2.60)	**100.00** Etanercept 50 mg QW		
6.01 (4.18 – 8.95)	6.01 (4.14 – 9.03)	5.01 (3.46 – 7.50)	4.63 (3.16 – 6.99)	4.07 (2.78 – 6.13)	3.95 (2.69 – 5.96)	3.83 (2.62 – 5.74)	3.69 (2.49 – 5.62)	3.64 (2.47 – 5.52)	1.96 (1.36 – 2.91)	1.12 (0.66 – 1.89)	**100.00** Etanercept 25 mg BIW	
43.23 (39.93 – 46.21)	43.22 (39.06 – 46.88)	36.03 (32.50 – 39.51)	33.3 (28.67 – 38.31)	29.24 (26.08 – 32.43)	28.41 (24.60 – 32.32)	27.49 (24.16 – 30.86)	26.52 (22.68 – 30.43)	26.16 (22.39 – 30.13)	14.07 (12.42 – 15.84)	8.04 (5.46 – 11.40)	7.18 (4.84 – 10.29)	**100.00** Placebo

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; Q2W, every two weeks; QW, once weekly.
Notes: RR >1 favours the treatment in the top left; grey shading denotes a difference at the standard benchmark of statistical significance (credible interval excluding 1).

Figure 13: League table summary of relative risks for the PASI 90 response at the end of induction analyses; baseline risk-adjusted; sensitivity analysis: decision set network

Ixekizumab 80 mg Q2W													
1.00 (0.89 – 1.15)	Guselkumab 100 mg												
1.20 (1.05 – 1.37)	1.21 (1.05 – 1.40)	Secukinumab 300 mg											
1.30 (1.11 – 1.55)	1.32 (1.11 – 1.59)	1.09 (0.91 – 1.31)	Infliximab 5 mg/kg										
1.45 (1.26 – 1.67)	1.46 (1.28 – 1.67)	1.21 (1.03 – 1.42)	1.11 (0.92 – 1.34)	Adalimumab 40 mg									
1.45 (1.08 – 2.18)	1.47 (1.09 – 2.20)	1.21 (0.89 – 1.83)	1.12 (0.80 – 1.70)	1.01 (0.76 – 1.46)	ABP501 40 mg								
1.52 (1.29 – 1.80)	1.54 (1.29 – 1.85)	1.27 (1.06 – 1.53)	1.17 (0.94 – 1.44)	1.05 (0.87 – 1.28)	1.05 (0.69 – 1.45)	Ustekinumab 90 mg							
1.57 (1.35 – 1.83)	1.59 (1.35 – 1.88)	1.31 (1.11 – 1.55)	1.20 (0.98 – 1.47)	1.08 (0.91 – 1.30)	1.08 (0.71 – 1.49)	1.03 (0.88 – 1.21)	Ustekinumab 45 mg						
1.62 (1.38 – 1.93)	1.64 (1.36 – 2.00)	1.35 (1.14 – 1.62)	1.24 (0.99 – 1.55)	1.12 (0.92 – 1.38)	1.11 (0.73 – 1.57)	1.06 (0.86 – 1.33)	1.03 (0.84 – 1.28)	Ustekinumab 45/90 mg					
1.66 (1.40 – 1.98)	1.68 (1.40 – 2.03)	1.38 (1.20 – 1.61)	1.27 (1.03 – 1.57)	1.15 (0.95 – 1.40)	1.14 (0.75 – 1.60)	1.09 (0.88 – 1.35)	1.06 (0.86 – 1.30)	1.03 (0.82 – 1.27)	Secukinumab 150 mg				
3.08 (2.69 – 3.54)	3.12 (2.65 – 3.66)	2.57 (2.20 – 3.01)	2.36 (1.94 – 2.86)	2.13 (1.79 – 2.53)	2.12 (1.40 – 2.91)	2.03 (1.69 – 2.43)	1.97 (1.65 – 2.33)	1.91 (1.54 – 2.32)	1.86 (1.53 – 2.25)	Etanercept 50 mg BIW			
5.27 (3.64 – 7.89)	5.33 (3.66 – 8.03)	4.40 (3.02 – 6.62)	4.04 (2.71 – 6.17)	3.64 (2.48 – 5.51)	3.60 (2.13 – 5.94)	3.46 (2.34 – 5.28)	3.36 (2.28 – 5.08)	3.26 (2.18 – 4.99)	3.17 (2.13 – 4.88)	1.71 (1.18 – 2.56)	Etanercept 50 mg QW		
6.08 (4.12 – 9.20)	6.15 (4.15 – 9.38)	5.07 (3.42 – 7.73)	4.66 (3.09 – 7.18)	4.20 (2.82 – 6.41)	4.15 (2.43 – 6.91)	4.00 (2.66 – 6.14)	3.87 (2.59 – 5.93)	3.76 (2.47 – 5.81)	3.67 (2.43 – 5.66)	1.97 (1.34 – 2.98)	1.15 (0.67 – 1.99)	Etanercept 25 mg BIW	
40.92 (36.62 – 42.87)	40.47 (36.24 – 44.13)	33.33 (29.72 – 36.79)	30.61 (26.03 – 35.24)	27.59 (24.38 – 30.81)	27.46 (18.42 – 36.62)	26.25 (22.43 – 30.16)	25.43 (22.10 – 28.81)	24.70 (20.70 – 28.76)	24.07 (20.36 – 27.96)	12.95 (11.35 – 14.62)	7.57 (5.09 – 10.88)	6.56 (4.36 – 9.61)	Placebo

Key: ABP501, adalimumab biosimilar; BIW, biweekly; PASI, Psoriasis Area Severity Index; Q2W, every two weeks; QW, once weekly.
Notes: RR >1 favours the treatment in the top left; grey shading denotes a difference at the standard benchmark of statistical significance (credible interval excluding 1).

PASI 75 response

A league table summary of RR outcomes from the baseline risk-adjusted NMA for PASI 75 response is provided as Figure 14.

As was observed in the PASI 90 response NMA, guselkumab demonstrates comparable or greater efficacy compared with alternative biologics at the end of induction. Specifically, guselkumab efficacy is similar to or greater than the IL-17 class of biologic treatment (RR versus ixekizumab = 0.98 [95% CrI: 0.93, 1.02]; RR versus secukinumab = 1.07 [95% CrI: 1.01, 1.13]) and greater than the anti-TNF (RR versus adalimumab = 1.24 [95% CrI: 1.18, 1.32]) and IL-12/23 classes (RR versus ustekinumab = 1.20-1.30 [95% CrI: 1.12, 1.41]).

Of note, PASI 75 was the only PASI response outcome for which the baseline risk-adjusted model was not the best fit. For this endpoint, the duration of psoriasis-adjusted model was shown to be the best fit, although both reported significant beta's (see Appendix D). As can be observed in the league table summary provided as Figure 15, RR outcomes from this model were consistent with those previously reported (RR versus ixekizumab = 0.93 [95% CrI: 0.87, 1.00], p[guselkumab better] = 3%; RR versus secukinumab = 1.02 [95% CrI: 0.94, 1.10], p[guselkumab better] = 66%; RR versus adalimumab = 1.37 [95% CrI: 1.26, 1.51], p[guselkumab better] = 100%; RR versus ustekinumab = 1.17-1.32 [95% CrI: 1.06, 1.53], p[guselkumab better] = 100%).

Figure 14: League table summary of relative risks for the PASI 75 response at the end of induction analyses; baseline risk-adjusted

Ixekizumab 80 mg Q2W												
1.02 (0.98 – 1.07)	Guselkumab 100 mg											
1.08 (1.02 – 1.15)	**1.06 (0.99 – 1.14)**	Infliximab 5 mg/kg										
1.09 (1.04 – 1.14)	1.07 (1.01 – 1.13)	**1.01 (0.94 – 1.08)**	Secukinumab 300 mg									
1.22 (1.15 – 1.30)	1.2 (1.12 – 1.29)	1.13 (1.05 – 1.22)	1.12 (1.05 – 1.21)	Ustekinumab 90 mg								
1.23 (1.16 – 1.32)	1.21 (1.13 – 1.30)	1.14 (1.05 – 1.24)	1.13 (1.07 – 1.20)	**1.01 (0.93 – 1.10)**	Secukinumab 150 mg							
1.27 (1.19 – 1.35)	1.24 (1.18 – 1.32)	1.17 (1.07 – 1.28)	1.17 (1.09 – 1.25)	1.04 (0.95 – 1.13)	1.03 (0.94 – 1.12)	Adalimumab 40 mg						
1.29 (1.22 – 1.38)	1.27 (1.18 – 1.37)	1.2 (1.10 – 1.30)	1.19 (1.11 – 1.28)	**1.06 (0.99 – 1.13)**	**1.05 (0.96 – 1.14)**	**1.02 (0.94 – 1.11)**	Ustekinumab 45 mg					
1.32 (1.24 – 1.43)	1.3 (1.21 – 1.41)	1.23 (1.12 – 1.35)	1.22 (1.13 – 1.32)	**1.09 (0.99 – 1.19)**	**1.07 (0.98 – 1.18)**	**1.04 (0.96 – 1.15)**	**1.03 (0.94 – 1.12)**	Ustekinumab 45/90 mg				
1.75 (1.65 – 1.86)	1.72 (1.60 – 1.85)	1.62 (1.50 – 1.75)	1.61 (1.51 – 1.73)	1.44 (1.33 – 1.55)	1.42 (1.31 – 1.54)	1.38 (1.27 – 1.51)	1.36 (1.26 – 1.47)	1.33 (1.21 – 1.45)	Etanercept 50 mg BIW			
2.44 (1.99 – 3.04)	2.4 (1.95 – 2.98)	2.26 (1.83 – 2.85)	2.24 (1.83 – 2.80)	2 (1.62 – 2.51)	1.98 (1.60 – 2.49)	1.93 (1.57 – 2.39)	1.89 (1.53 – 2.37)	1.85 (1.49 – 2.31)	1.39 (1.13 – 1.73)	Etanercept 50 mg QW		
2.45 (2.05 – 3.01)	2.41 (2.00 – 2.97)	2.27 (1.89 – 2.79)	2.26 (1.88 – 2.76)	2.01 (1.67 – 2.47)	1.99 (1.65 – 2.46)	1.94 (1.60 – 2.40)	1.9 (1.58 – 2.34)	1.85 (1.53 – 2.30)	1.4 (1.17 – 1.71)	**1 (0.76 – 1.35)**	Etanercept 25 mg BIW	
16.67 (16.23 – 17.04)	16.37 (15.74 – 16.92)	15.44 (14.48 – 16.35)	15.32 (14.69 – 15.91)	13.66 (12.81 – 14.41)	13.53 (12.67 – 14.33)	13.15 (12.43 – 13.86)	12.92 (12.12 – 13.64)	12.6 (11.67 – 13.45)	9.51 (8.94 – 10.07)	6.82 (5.49 – 8.35)	6.79 (5.55 – 8.13)	Placebo

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; Q2W, every two weeks; QW, once weekly.
Notes: RR >1 favours the treatment in the top left; grey shading denotes a difference at the standard benchmark of statistical significance (credible interval excluding 1).

Figure 15: League table summary of relative risks and p[guselkumab better] for the PASI 75 response at the end of induction analyses; duration of psoriasis-adjusted

5.51 Infliximab 5 mg/kg												
1.01 (0.93 – 1.08)	**3.18** Ixekizumab 80 mg Q2W											
1.08 (0.98 – 1.18)	1.07 (0.996 – 1.15)	**NA** Guselkumab 100 mg										
1.1 (1.01 – 1.19)	1.08 (1.03 – 1.15)	1.02 (0.94 – 1.10)	**65.80** Secukinumab 300 mg									
1.24 (1.12 – 1.38)	1.23 (1.14 – 1.34)	1.15 (1.05 – 1.28)	1.13 (1.07 – 1.21)	**99.70** Secukinumab 150 mg								
1.27 (1.13 – 1.42)	1.25 (1.15 – 1.37)	1.17 (1.06 – 1.31)	1.15 (1.06 – 1.27)	1.02 (0.92 – 1.13)	**99.84** Ustekinumab 90 mg							
1.36 (1.21 – 1.53)	1.35 (1.23 – 1.48)	1.26 (1.13 – 1.42)	1.24 (1.13 – 1.37)	1.1 (0.98 – 1.23)	1.08 (1.01 – 1.15)	**100.00** Ustekinumab 45 mg						
1.42 (1.26 – 1.64)	1.4 (1.27 – 1.61)	1.32 (1.17 – 1.53)	1.29 (1.18 – 1.48)	1.14 (1.02 – 1.32)	1.13 (0.98 – 1.31)	1.04 (0.91 – 1.22)	**100.00** Ustekinumab 45/90 mg					
1.48 (1.31 – 1.67)	1.46 (1.30 – 1.66)	1.37 (1.26 – 1.51)	1.35 (1.19 – 1.52)	1.19 (1.03 – 1.36)	1.17 (1.02 – 1.33)	1.09 (0.94 – 1.24)	1.04 (0.89 – 1.20)	**100.00** Adalimumab 40 mg				
1.81 (1.61 – 2.04)	1.79 (1.63 – 1.98)	1.68 (1.49 – 1.90)	1.65 (1.50 – 1.82)	1.46 (1.32 – 1.61)	1.43 (1.30 – 1.58)	1.33 (1.20 – 1.48)	1.27 (1.10 – 1.45)	1.23 (1.07 – 1.43)	**100.00** Etanercept 50 mg BIW			
2.59 (2.02 – 3.33)	2.55 (2.03 – 3.26)	2.39 (1.88 – 3.11)	2.35 (1.87 – 3.01)	2.08 (1.65 – 2.66)	2.04 (1.63 – 2.60)	1.89 (1.51 – 2.42)	1.81 (1.40 – 2.34)	1.75 (1.35 – 2.31)	1.43 (1.17 – 1.77)	**100.00** Etanercept 25 mg BIW		
3.17 (2.32 – 4.27)	3.13 (2.32 – 4.20)	2.94 (2.16 – 3.96)	2.89 (2.15 – 3.87)	2.55 (1.89 – 3.44)	2.5 (1.88 – 3.35)	2.33 (1.74 – 3.12)	2.22 (1.64 – 3.00)	2.15 (1.57 – 2.93)	1.75 (1.33 – 2.31)	1.23 (0.86 – 1.71)	**100.00** Etanercept 50 mg QW	
16.8 (15.34 – 17.72)	16.54 (15.87 – 17.07)	15.52 (14.40 – 16.40)	15.24 (14.33 – 16.03)	13.47 (12.25 – 14.59)	13.24 (11.95 – 14.35)	12.27 (11.10 – 13.48)	11.76 (10.16 – 13.13)	11.32 (9.96 – 12.65)	9.24 (8.21 – 10.29)	6.47 (5.02 – 8.23)	5.27 (3.90 – 7.18)	**100.00** Placebo

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; Q2W, every two weeks; QW, once weekly.
Notes: RR >1 favours the treatment in the top left; grey shading denotes a difference at the standard benchmark of statistical significance (credible interval excluding 1).

Safety outcomes

A league table summary of RR outcomes from the baseline risk-adjusted NMA for AE rate is provided as Figure 16. For safety analyses a relative risk less than 1 favours guselkumab.

Guselkumab demonstrates comparable AE rates to those associated with alternative biologics at the end of induction with RR ranging from 1.08 versus etanercept (50mg once weekly) to 0.81 versus infliximab (RR versus ixekizumab = 0.89 [95% CrI: 0.80, 1.00]; RR versus secukinumab = 0.91 [95% CrI: 0.81, 1.04; RR versus adalimumab = 0.96 [95% CrI: 0.88, 1.06]; RR versus ustekinumab = 0.95-1.04 [95% CrI: 0.84, 1.19]). Interpretation of SAE and WDAE rate analyses are limited by the small event numbers but also generally show no meaningful differences across treatments (see Appendix D).

Of note, the best model fit for the AE rate outcome was the unadjusted model (see Appendix D); the league table for this analysis is provided in Appendix D. RR outcomes from this model were consistent with those previously reported (RR versus ixekizumab = 0.90 [95% CrI: 0.80, 1.02], p[guselkumab better] = 96%; RR versus secukinumab = 0.92 [95% CrI: 0.82, 1.04], p[guselkumab better] = 88%; RR versus adalimumab = 0.98 [95% CrI: 0.90, 1.08], p[guselkumab better] = 64%; RR versus ustekinumab = 0.96-1.05 [95% CrI: 0.85, 1.29], p[guselkumab better] = 22-69%).

Figure 16: League table summary of relative risks for the AE rate at the end of induction analyses; baseline risk-adjusted

Placebo											
1.02 (0.86 – 1.23)	Etanercept 50 mg QW										
0.98 (0.91 – 1.07)	0.97 (0.79 – 1.16)	Ustekinumab 90 mg									
0.95 (0.87 – 1.04)	0.93 (0.75 – 1.13)	0.96 (0.84 – 1.09)	Guselkumab 100 mg								
0.93 (0.87 – 1.01)	0.92 (0.74 – 1.11)	0.95 (0.87 – 1.04)	0.99 (0.87 – 1.11)	Ustekinumab 45 mg							
0.91 (0.86 – 0.97)	0.89 (0.73 – 1.07)	0.93 (0.83 – 1.02)	0.96 (0.88 – 1.06)	0.97 (0.88 – 1.07)	Adalimumab 40 mg						
0.9 (0.85 – 0.95)	0.88 (0.74 – 1.05)	0.92 (0.84 – 1.00)	0.95 (0.85 – 1.06)	0.97 (0.89 – 1.05)	0.99 (0.91 – 1.07)	Etanercept 50 mg BIW					
0.9 (0.83 – 0.97)	0.88 (0.73 – 1.06)	0.91 (0.82 – 1.02)	0.95 (0.84 – 1.07)	0.96 (0.86 – 1.07)	0.99 (0.90 – 1.09)	1 (0.91 – 1.08)	Ustekinumab 45/90 mg				
0.86 (0.81 – 0.93)	0.85 (0.70 – 1.03)	0.88 (0.79 – 0.97)	0.91 (0.81 – 1.04)	0.93 (0.84 – 1.02)	0.95 (0.87 – 1.04)	0.96 (0.89 – 1.04)	0.96 (0.88 – 1.05)	Secukinumab 300 mg			
0.84 (0.80 – 0.90)	0.83 (0.68 – 0.99)	0.86 (0.78 – 0.95)	0.89 (0.80 – 1.00)	0.91 (0.82 – 0.99)	0.93 (0.85 – 1.02)	0.94 (0.88 – 1.00)	0.94 (0.86 – 1.03)	0.98 (0.90 – 1.06)	Ixekizumab 80 mg Q2W		
0.84 (0.79 – 0.91)	0.83 (0.68 – 1.00)	0.86 (0.77 – 0.96)	0.89 (0.79 – 1.00)	0.91 (0.82 – 1.00)	0.93 (0.84 – 1.04)	0.94 (0.87 – 1.02)	0.94 (0.85 – 1.05)	0.98 (0.91 – 1.07)	1 (0.92 – 1.10)	Secukinumab 150 mg	
0.76 (0.71 – 0.84)	0.75 (0.61 – 0.91)	0.78 (0.69 – 0.88)	0.81 (0.72 – 0.93)	0.82 (0.74 – 0.93)	0.84 (0.76 – 0.94)	0.84 (0.78 – 0.95)	0.85 (0.76 – 0.96)	0.88 (0.80 – 1.00)	0.9 (0.82 – 1.02)	0.9 (0.81 – 1.03)	Infliximab 5 mg/kg

Key: AE, adverse event; BIW, biweekly; PASI, Psoriasis Area Severity Index; Q2W, every two weeks; QW, once weekly.
Notes: RR <1 favours the treatment in the top left; grey shading denotes a difference at the standard benchmark of statistical significance (credible interval excluding 1).

Risk difference analyses

Pairwise comparisons versus guselkumab from risk difference analyses are provided in Appendix D.

The risk difference NMAs corroborate the relative effects NMAs with guselkumab demonstrating generally comparable or greater efficacy and tolerability compared with alternative biologics across outcomes.

For the primary trial endpoint of PASI 90 and PASI 75 response at the end of induction, respectively, guselkumab demonstrated comparability or superiority to the IL-17 class of biologic treatment (RD% versus ixekizumab = -0.72 [95% CrI: -9.16, 7.65] and -2.95% [-8.83, 3.02]; RD% versus secukinumab = 11.40 [95% CrI: 3.03, 19.87] and 6.28 [95% CrI: 0.10, 12.31]) and superiority to the anti-TNF (RD% versus adalimumab = 23.39 [16.36, 30.52] and 17.70 [12.28, 23.22]) and IL-12/23 classes (RD% versus ustekinumab = 24.32-26.57 [95% CrI: 15.59, 35.40] and 15.16-19.17 [95% CrI: 8.90, 25.40]).

Uncertainties in the indirect and mixed treatment comparisons

Considerable efforts were taken to explore the presence and impact of between-study heterogeneity among the studies identified from the SLR for inclusion in NMAs. Inspection of bar charts, scatterplots, and evidence tables (see Appendix D) identified several aspects of between-study heterogeneity that included both clinical demographic measures as well as variations in placebo group event rates, both of which can result in misleading estimates of treatment effect if unaccounted for in network analyses.[67]

To address these challenges in the analyses of clinical outcomes, meta-regression models as outlined by existing methodological guidance[64] were performed and inspection of model fit measures was conducted to identify the most reliable estimates of treatment effect. The baseline risk-adjusted NMA, accounting for variations in placebo group risk, provided the best fit for most endpoints, including the PASI 90 response data, and therefore was selected as the main analysis. It is important to note that studies without a placebo arm were not excluded from the baseline risk-adjusted NMAs. As per baseline risk-adjustment methods outlined by

NICE[63], the same interaction effect was assumed for all treatments compared to placebo. That is, the regression terms for the baseline risk-adjustment NMA will cancel for all other comparisons, so no baseline risk-adjustment was performed for trials that do not include placebo arm.

Reassuringly, results from the baseline risk-adjusted NMAs were largely aligned with direct estimates from active comparator trials. Further analyses using risk difference as opposed to relative effects further supported the baseline risk-adjusted NMA outcomes, underscoring the importance of adjusting for cross-trial differences and lending credibility to the approach of selecting the best fitting models when interpreting results on the relative scale.

Conclusion

Overall, the consistent outcome for guselkumab was one of comparable or greater clinical efficacy and generally similar tolerability versus alternative biologics used in current practice, at the end of treatment induction. More specifically, the efficacy NMA showed that guselkumab is superior to anti-TNF (including adalimumab), IL-12/23 ustekinumab and IL-17 secukinumab, and non-inferior to IL-17 ixekizumab. The safety NMA indicated that guselkumab has a similar safety profile to other biologics, regardless of treatment class. The results of the NMA are aligned with the results of guselkumab phase III programme, supporting the superior efficacy of guselkumab over adalimumab and the similarity of the safety profile.

Any differences in key endpoints of PASI 90 response, PASI 75 response and AE rates that fell within the standard benchmark of statistical significance across baseline risk-adjusted relative effects and risk difference NMAs, were all in favour of guselkumab.

B.3.10. Adverse reactions

Summary of safety data from VOYAGE 1

A summary of the safety events at Week 16 and Week 48 from the Phase III RCT VOYAGE 1 is provided in Table 15. Subcutaneous guselkumab at a dose of 100mg was generally well tolerated. The proportion of patients with AEs and serious adverse events (SAEs) were comparable across treatment groups at both Week 16

and Week 48. Similarly, the proportion of patients who discontinued due to AEs was comparable at Week 16 and Week 48 across treatment groups. No deaths occurred during the placebo-controlled period (Week 0–16). However, through Week 48, one adalimumab-treated patient died of staphylococcal pneumonia following a prolonged hospitalisation that was initially due to ischaemic hepatitis.

Table 15: Summary of key safety events from VOYAGE 1

	Week 0–16			Week 16–48	Week 0–48	
	PBO	GUS	ADA	PBO-GUS	GUS	ADA
Patients treated, n	174	329	333	165	329	333
Average duration of follow-up (weeks)	15.88	16.27	16.14	31.88	46.47	45.56
Average exposure (number of administrations)	10.66	10.81	10.75	20.61	30.32	29.58
Patients with an AE, n (%)	86 (49.4)	170 (51.7)	170 (51.1)	107 (64.8)	243 (73.9)	248 (74.5)
Patients with a SAE, n (%)	3 (1.7)	8 (2.4)	6 (1.8)	5 (3.0)	16 (4.9)	15 (4.5)
Patients who died, n	0	0	0	0	0	1
Discontinuations due to an AE, n (%)	3 (1.7)	8 (2.4)	6 (1.8)	5 (3.0)	16 (4.9)	15 (4.5)

Key: ADA, adalimumab; AE, adverse event; GUS, guselkumab; PBO, placebo; SAE, serious adverse event.
Source: Blauvelt *et al*., 2017[53]; VOYAGE 1 CSR[57]

Common AEs emerging with guselkumab treatment in VOYAGE 1 (≥5% of patients in any treatment group) at both Week 16 and Week 48 were nasopharyngitis, upper respiratory tract infection (URTI), headache, arthralgia, pruritus and back pain, as summarised in Table 16. SAEs that occurred at both Week 16 and Week 48 in patients treated with guselkumab were predominantly events of: cardiac disorders; infections and infestations; and injury, poisoning and procedural complications, as summarised in Table 16. This safety profile was similar to that observed with adalimumab treatment, with no new safety signals associated with the use of IL-23 inhibitor treatment compared to alternative biologics observed.

Table 16: Treatment-emergent adverse events with frequency ≥5% and serious adverse events in VOYAGE 1

	Week 0-16			Week 16-48	Week 0-48	
	PBO	GUS	ADA	PBO-GUS	GUS	ADA
Any AE, n (%)	86 (49.4)	170 (51.7)	170 (51.1)	107 (64.8)	243 (73.9)	248 (74.5)
Nasopharyngitis	17 (9.8)	30 (9.1)	35 (10.5)	34 (20.6)	83 (25.2)	74 (22.2)
URTI	9 (5.2)	25 (7.6)	16 (4.8)	17 (10.3)	47 (14.3)	42 (12.6)
Injection-site erythema	1 (0.6)	6 (1.8)	15 (4.5)	3 (1.8)	8 (2.4)	22 (6.6)
Headache	7 (4.0)	12 (3.6)	13 (3.9)	1 (0.6)	18 (5.5)	25 (7.5)
Arthralgia	3 (1.7)	11 (3.3)	9 (2.7)	2 (1.2)	18 (5.5)	16 (4.8)
Pruritus	10 (5.7)	5 (1.5)	7 (2.1)	0	8 (2.4)	12 (3.6)
Back pain	2 (1.1)	6 (1.8)	4 (1.2)	1 (0.6)	12 (3.6)	17 (5.1)
Any SAE, n (%)	3 (1.7)	8 (2.4)	6 (1.8)	5 (3.0)	16 (4.9)	15 (4.5)
Cardiac disorders	0	1 (0.3)	2 (0.6)	1 (0.6)	1 (0.3)	3 (0.9)
Infections and infestations	0	0	2 (0.6)	1 (0.6)	2 (0.6)	5 (1.5)
Injury, poisoning and procedural complications	0	1 (0.3)	2 (0.6)	1 (0.6)	1 (0.3)	4 (1.2)
Vascular disorders	0	0	1 (0.3)	0	0	1 (0.3)
General disorders and administration site conditions	0	1 (0.3)	0	0	1 (0.3)	0
Hepatobiliary disorders	0	1 (0.3)	0	0	1 (0.3)	2 (0.6)
Musculoskeletal and connective tissue disorders	1 (0.6)	1 (0.3)	0	1 (0.6)	1 (0.3)	1 (0.3)
Nervous system disorders	0	1 (0.3)	0	0	1 (0.3)	0
Psychiatric disorders	1 (0.6)	1 (0.3)	0	0	1 (0.3)	1 (0.3)
Renal and urinary disorders	0	1 (0.3	0	0	3 (0.9)	0
Skin and subcutaneous tissue disorders	1 (0.6)	0	0	1 (0.6)	0	1 (0.3)
Congenital, familial and genetic disorders	0	0	0	0	1 (0.3)	0
Gastrointestinal disorders	0	0	0	1 (0.6)	2 (0.6)	0

	Week 0-16			Week 16-48	Week 0-48	
	PBO	GUS	ADA	PBO-GUS	GUS	ADA
Neoplasms benign, malignant and unspecified	0	0	0	0	1 (0.3)	0
Key: ADA, adalimumab; AE, adverse event; GUS, guselkumab; PBO, placebo; SAE, serious adverse event; URTI, upper respiratory tract infection. **Source:** Blauvelt *et al*., 2017[53]; VOYAGE 1 CSR[57]						

Summary of safety data from VOYAGE 2

A summary of the safety events during the placebo-controlled period (Weeks 0–16), the active-comparator period (Weeks 0–28), and the randomised withdrawal and retreatment period (Weeks 28–48) for the Phase III RCT, VOYAGE 2 is provided in Table 17. Subcutaneous guselkumab at a dose of 100mg was generally well tolerated. As observed in VOYAGE 1, the proportion of patients with AEs and SAEs were comparable across treatment groups during each study period. Similarly, the proportion of patients who discontinued due to AEs was comparable across treatment groups during each study period. No deaths occurred through Week 48 of this study.

Table 17: Summary of key safety events from VOYAGE 2

	Week 0–16			16–28	Week 0–28		Week 28–48	
	Placebo-controlled period				Active comparator-controlled period		Randomised withdrawal and retreatment period	
	PBO	GUS	ADA	PBO to GUS	GUS	ADA	MA[a]	WD[b]
Patients treated	248	494	248	233	494	248	192	182
Average duration of follow-up (weeks)	15.89	16.14	16.07	11.95	27.70	27.45	20.02	19.47
Average exposure (number of administrations)	10.60	10.74	10.67	5.93	16.48	16.28	4.95	4.93
Patients with an AE, n (%)	111 (44.8)	235 (47.6)	120 (48.4)	78 (33.5)	288 (58.3)	156 (62.9)	99 (51.6)	81 (44.5)

Patients with a SAE, n (%)	3 (1.2)	8 (1.6)	6 (2.4)	4 (1.7)	18 (3.6)	9 (3.6)	2 (1.0)	3 (1.6)
Patients who died, n	0	0	0	0	0	0	0	0
Discontinuations due to an AE, n (%)	2 (0.8)	7 (1.4)	4 (1.6)	1 (0.4)	11 (2.2)	6 (2.4)	0	0

Key: ADA, adalimumab; GUS, guselkumab; MA, maintenance; PASI, Psoriasis Severity Index; PASI 90, 90% or greater improvement in PASI score from baseline; PBO, placebo; q8w, every 8 weeks; WD, withdrawal.
Notes: [a], includes patients treated with guselkumab at Week 0-28, PASI 90 responders re-randomised at Week 28 to continue guselkumab 100mg q8w; [b], includes patients treated with guselkumab at Week 0–28, PASI 90 responders re-randomised at Week 28 to placebo (withdrawal), then retreated with guselkumab 100mg q8w after ≥50% loss of Week 28 PASI 90.
Source: Reich *et al*., 2017[54]; VOYAGE 2 CSR[58]

Common AEs emerging with guselkumab treatment in VOYAGE 2 (≥5% of patients in any treatment group) during each study period were nasopharyngitis, headache and URTI, as summarised in Table 18. As with VOYAGE 1, guselkumab treatment was associated with very few SAEs, and those that did occur during both the placebo-controlled period (Weeks 0–16) and the active-comparator period (Weeks 0–28) were predominantly events of cardiac disorders, infections and infestations, musculoskeletal and connective tissue disorders and gastrointestinal disorders. SAEs that occurred in the randomised withdrawal and retreatment period were predominantly events of infections and infestations, as summarised in Table 18.

Table 18: Treatment-emergent adverse events with frequency ≥5% and serious adverse events in VOYAGE 2

	Week 0–16			Week 16–28	Week 0–28		Week 28–48	
	Placebo-controlled period				Active comparator-controlled period		Randomised withdrawal and retreatment period	
	PBO (n=248)	GUS (n=494)	ADA (n=248)	PBO to GUS (n=233)	GUS (n=494)	ADA (n=248)	Maintenance[a] (n=192)	Withdrawal[b] (n=182)
Any adverse event, n (%)	111 (44.8)	235 (47.6)	120 (48.4)	78 (33.5)	288 (58.3)	156 (62.9)	99 (51.6)	81 (44.5)
Nasopharyngitis	16 (6.5)	35 (7.1)	20 (8.1)	12 (5.2)	51 (10.3)	34 (13.7)	22 (11.5)	23 (12.6
Headache	7 (2.8)	25 (5.1)	5 (2.0)	5 (2.1)	29 (5.9)	9 (3.6)	3 (1.6)	2 (1.1)
URTI	10 (4.0)	16 (3.2)	4 (1.6)	5 (2.1)	25 (5.1)	10 (4.0)	9 (4.7)	10 (5.5)
Any SAE, n (%)	3 (1.2)	8 (1.6)	6 (2.4)	4 (1.7)	18 (3.6)	9 (3.6)	2 (1.0)	3 (1.6)
Cardiac disorders	0	2 (0.4)	2 (0.8)	0	5 (1.0)	2 (0.8)	-	-
Infections and infestations	0	1 (0.2)	2 (0.8)	1 (0.4)	3 (0.6)	3 (1.2)	2 (1.0)	0
Injury, poisoning and procedural complications	0	0	0	3 (1.3)	0	0	0	0
General disorders and administration site conditions	0	1 (0.2)	0	0	1 (0.2)	0	0	1 (0.5)
Hepatobiliary disorders	1 (0.4)	0	0	0	1 (0.2)	0		
Musculoskeletal and connective tissue disorders	1 (0.4)	1 (0.2)	1 (0.4)	0	1 (0.2)	2 (0.8)	0	1 (0.5)
Nervous system disorders	0	1 (0.2)	0	1 (0.4)	1 (0.2)	1 (0.4)	0	0
Psychiatric disorders	0	0	1 (0.4)	0	0 (0)	1 (0.4)	0	0
Renal and urinary disorders	0	1 (0.2)	0	0	1 (0.2)	0	0	0
Gastrointestinal disorders	1 (0.4)	0	2 (0.8)	0	1 (0.2)	2 (0.8)	0	0
Neoplasms benign, malignant and unspecified	0	0	0	0	1 (0.2)	0	0	0
Investigations	0	1 (0.2)	0	0	1 (0.2)	0	0	0

	Week 0–16			Week 16–28	Week 0–28		Week 28–48	
	Placebo-controlled period				Active comparator-controlled period		Randomised withdrawal and retreatment period	
	PBO (n=248)	GUS (n=494)	ADA (n=248)	PBO to GUS (n=233)	GUS (n=494)	ADA (n=248)	Maintenance[a] (n=192)	Withdrawal[b] (n=182)
Blood and lymphatic system disorders	0	0	0	1 (0.4)	1 (0.2)	0	0	0
Immune system disorders	0	0	0	1 (0.4)	0	0	0	0
Reproductive system and breast disorders	0	0	0	0	1 (0.2)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	0	0	1 (0.5%)

Key: ADA, adalimumab; GUS, guselkumab; PASI, Psoriasis Severity Index; PASI 90, 90% or greater improvement in PASI score from baseline; PBO, placebo; q8w, every 8 weeks; SAE, serious adverse event; URTI, upper respiratory tract infection.
Notes: [a], includes patients treated with guselkumab at Week 0–8, PASI 90 responders re-randomised at Week 28 to continue guselkumab 100mg q8w; [b], includes patients treated with guselkumab at Week 0–28, PASI 90 responders re-randomised at Week 28 to placebo (withdrawal), then retreated with guselkumab 100mg q8w after ≥50% loss of Week 28 PASI 90.
Source: Reich *et al*., 2017[54]; VOYAGE 2 CSR[58]

Pooled safety data from VOYAGE 1 and VOYAGE 2

Through Week 100, pooled safety data from the VOYAGE 1 and VOYAGE 2 studies demonstrated that the overall safety event rates among the guselkumab-treated patients were comparable through Year 1 and cumulatively through Year 2, as summarised in Table 19. Additionally, safety data from adalimumab-treated patients who crossed over to guselkumab were consistent with overall guselkumab safety data, with no additional safety signals identified.

Guselkumab was well tolerated for up to 2 years of continuous treatment, with no disproportionate increases in rates of AEs or SAEs compared with rates reported through Week 48, and a similar safety profile observed with no tuberculosis, opportunistic infections, or serious hypersensitivity reactions reported.

Table 19: Summary of key safety events from VOYAGE 1 and VOYAGE (values reported as events/100 patient years)

	Guselkumab through Year 1[a]	**Guselkumab through Year 2[a]**
N	[redacted]	[redacted]
Total patient years of follow-up	[redacted]	[redacted]
Number of AEs	[redacted]	[redacted]
Most common AE Nasopharyngitis URTI Bronchitis	[redacted]	[redacted]
AEs leading to withdrawal	[redacted]	[redacted]
SAE	[redacted]	[redacted]
Infections Requiring treatment Serious infection	[redacted]	[redacted]
Malignancies excluding NMSC (95% CI)	[redacted]	[redacted]
NMSC (95% CI)	[redacted]	[redacted]
MACE[b] (95% CI)	[redacted]	[redacted]

Key: AE, adverse event; CI, confidence interval; MACE, major adverse cardiac event; NMSC, nonmelanoma skin cancer; SAE, serious adverse event; URTI, upper respiratory tract infection.
Notes: [a], includes patients initially randomised to placebo who crossed over to guselkumab at Week 16; [b], MACE events adjudicated for Year 1 and investigator reported for Year 2.
Source: Data on file

Through Week 100, there were no disproportionate increases in rates of AEs compared with rates reported through Week 48. Serious AE rates were low and remained stable; no tuberculosis, opportunistic infections, or serious hypersensitivity reactions were reported.

Summary of safety data from NAVIGATE

Week 0 though Week 60

A summary of the safety events occurring during the open-label ustekinumab treatment period (Weeks 0–16), the continued open-label ustekinumab treatment period and the randomised active-treatment period (Weeks 16-60) for the Phase III trial, NAVIGATE is provided in Table 20. Guselkumab was generally well tolerated. The proportion of randomised patients experiencing one or more AEs from Week 16 through to Week 60 was slightly higher in the guselkumab group compared to the ustekinumab group. However, the rates of discontinuations due to AEs were similar between treatment groups, and no pattern of AEs leading to discontinuation was observed as most were reported as single events. These results were consistent with the data reported from Week 16 though Week 40. No deaths occurred during the open-label ustekinumab treatment period (Week 0–16). Two deaths occurred during the continued open-label ustekinumab treatment period and the randomised active-treatment period (Weeks 16–60). One patient in the non-randomised ustekinumab continuation group died due to metastatic pancreatic carcinoma; one patient in the guselkumab treated group died due to squamous cell carcinoma of the neck.

Table 20: Summary of key safety events from NAVIGATE

	Week 0–16	Week 16–40			Week 16–60		
		Non-R patients	Patients randomised at Week 16		Non-R patients	Patients randomised at Week 16	
	Open-label UST	Open-label UST	GUS	UST	Open-label UST	GUS	UST
Patients treated	871	585	135	133	585	135	133
Average duration of follow-up (weeks)	16.16	24.02	23.81	23.01	-	42.22	40.63
Average exposure (number of administrations)	1.99	1.99	3.89	3.76	-	5.76	5.49
Patients with an AE, n (%)	254 (29.2)	171 (29.2)	73 (54.1)	62 (46.6)	242 (41.4)	87 (64.4)	74 (55.6)
Patients with a SAE, n (%)	11 (1.3%)	13 (2.2)	5 (3.7)	2 (1.5)	20 (3.4)	9 (6.7)	6 (4.5)
Patients who died, n	0	1	1	0	1	0	0
Patients who discontinued due to an AE, n (%)	2 (0.2)	7 (1.2)	3 (2.2)	2 (1.5)	7 (1.2)	3 (2.2)	2 (1.5)

Key: AE, adverse event; GUS, guselkumab; R, randomised; SAE, serious adverse event; UST, ustekinumab.
Source: Langley *et al*.,2017[56], NAVIGATE CSR[59], NAVIGATE CSR 60-week follow up[68]

Common AEs emerging with both guselkumab and ustekinumab treatment in NAVIGATE (≥5% of patients in any treatment group) from Week 16 through Week 60 were nasopharyngitis and URTIs, as summarised in Table 21. The proportion of patients randomised at Week 16 who experienced one or more SAE through Week 60 were low for both guselkumab treated and ustekinumab treated groups. Furthermore, no particular pattern of SAEs was observed and most SAEs reported were singular events (Table 21).

Table 21: Treatment-emergent adverse events with frequency ≥5% and serious adverse events in NAVIGATE

	Week 0-16	Week 16–40			Week 16–60		
		Non-R pts	Patients randomised at Week 16		Non-R pts	Patients randomised at Week 16	
	Open-label UST (n=871)	Open-label UST (n=585)	GUS (n=135)	UST (n=133)	Open-label UST (n=585)	GUS (n=135)	UST (n=133)
Any AE, n (%)	254 (29.2)	171 (29.2)	73 (54.1)	62 (46.6)	242 (41.4)	87 (64.4)	74 (55.6)
Nasopharyngitis	47 (5.4)	13 (2.2)	18 (13.3)	13 (9.8)	33 (5.6)	23 (17.0%)	23 (17.3%)
URTI	33 (3.8)	12 (2.1)	10 (7.4)	5 (3.8)	27 (4.6)	15 (11.1)	11 (8.3)
Any SAE, n (%)	11 (1.3)	13 (2.2)	5 (3.7)	2 (1.5)	20 (3.4)	9 (6.7)	6 (4.5)
Cardiac disorders	1 (0.1)	2 (0.3)	2 (1.5)	1 (0.8)	2 (0.3)	2 (1.5)	1 (0.8)
Infections and infestations	3 (0.3)	2 (0.3)	-	-	5 (0.9)	1 (0.7)	0
Injury, poisoning and procedural complications	2 (0.2)	2 (0.3)	1 (0.7)	0	2 (0.3)	1 (0.7)	0
General disorders and administration site conditions	-	1 (0.2)	-	-	2 (0.3)	-	-
Hepatobiliary disorders	1 (0.1)	1 (0.2)	-	-	1 (0.2)	-	-
Musculoskeletal and connective tissue disorders	-	1 (0.2)	0	1 (0.8)	1 (0.2)	0	1 (0.8)
Nervous system disorders	1 (0.1)	-	-	-	-	1 (0.7)	0
Gastrointestinal disorders	-	1 (0.2)	-	-	3 (0.5)	-	-
Neoplasms benign, malignant and unspecified	-	2 (0.3)	1 (0.7)	0	2 (0.3)	2 (1.5)	0
Pregnancy, puerperium and perinatal conditions	-	-	1 (0.7)	0	-	2 (1.5)	0
Skin and subcutaneous tissue disorders	2 (0.2)	-	-	-	-	0	1 (0.8)

	Week 0-16	Week 16–40			Week 16–60		
		Non-R pts	Patients randomised at Week 16		Non-R pts	Patients randomised at Week 16	
	Open-label UST (n=871)	Open-label UST (n=585)	GUS (n=135)	UST (n=133)	Open-label UST (n=585)	GUS (n=135)	UST (n=133)
Eye disorders	1 (0.1)	2 (0.3)	-	-	3 (0.5)	0	1 (0.8)
Metabolism and nutrition disorders	-	-	-	-	-	0	1 (0.8)
Blood and LS disorders	-	-	-	-	1 (0.2)	-	-

Key: AE, adverse event; GUS, guselkumab; pts, patients; LS, lymphatic system; R, randomised; SAE, serious adverse event; URTI, upper respiratory tract infection; UST, ustekinumab.
Source: Langley *et al.*,2017[56], NAVIGATE CSR[59], NAVIGATE CSR 60-week follow up[68]

B.3.11. Areas of uncertainty

There are some areas of uncertainty in the evidence base with consideration of the decision problem that should be addressed, including the trial populations versus the target population, and the need for an indirect comparison. These areas of uncertainty are further discussed below:

The VOYAGE and NAVIGATE trials enrolled patients who were candidates for phototherapy or systemic treatment, which is a slightly broader population than those for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. However, the baseline characteristics of participants enrolled are reflective of patients who would be considered for biologic treatment in clinical practice: all patients had severe disease in line with previous NICE technology appraisal definitions (PASI ≥10 and DLQI >10); and the majority had disease which was inadequately controlled with topical agents, phototherapy and non-biologic systemic treatment, with less than 20% of randomised patients across trials being naïve to conventional systemic therapy (administered at third-line in current practice) and biologic treatment.

Of note, the evidence base provides data across patients who are biologic-naïve, and patients who have previously been exposed to biologic treatments. The

positioning for guselkumab in the NHS is as a first-choice biologic based on the clinical- and cost-comparison evidence presented in this submission. However, patients who are already receiving biologic treatment in current practice may also benefit from switching to guselkumab as a new treatment class and the data also supports such use. Importantly, pre-specified subgroup analyses confirm a consistent benefit in favour of guselkumab regardless of disease severity at baseline and treatment history.

B.3.12. Conclusions about comparable health benefits and safety

The target population for guselkumab in the NHS is for the treatment of adults with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated. In current practice, such patients may be treated with TNF-α inhibitors (etanercept, infliximab, adalimumab), ustekinumab, ixekizumab or secukinumab.

Guselkumab offers a new mechanism of action to these treatments (IL-23) that provides a more targeted and upstream blockage of inflammatory pathways involved in psoriasis lesion formation, and delivers sustained and symptom free skin clearance leading to normalised patient quality of life, reduced comorbidities (anxiety and depression) and improved work productivity. The value of having a range of treatments with different mechanisms of action available was recently acknowledged by NICE.[8]

In the head-to-head VOYAGE trial programme (with data up to Week 100), guselkumab demonstrated superiority over the TNF-α inhibitor, adalimumab, which is a market leader in psoriasis biologics with [redacted] of the market share (see Section B.4.2). This superiority covered a clinically meaningful improvement in the treatment aim of achieving and sustaining a PASI 75 response, and the treatment goal of achieving and sustaining a PASI 90 response and improving disease-specific quality of life, with many patients reporting no impact of disease on their quality of life, including daily activities, leisure, work and school and personal relationships (as measured by the DLQI). Importantly, many patients also experienced clinically meaningful improvements in signs and symptoms of disease (as measured by the PSSD) with many becoming sign and symptom free. Significant improvements in the

ability to perform physical, cognitive and occupational tasks (as measured by the SF-36 and WLQ), and improved mental health with regard to anxiety and depression (as measured by HADS) was also observed.

With regards to safety and tolerability, guselkumab demonstrated comparability to both active treatments and placebo, with an AE profile comparable to that of adalimumab and ustekinumab (as observed in the NAVIGATE trial) which have fully established themselves as safe treatments for plaque psoriasis in clinical practice. There were no new safety signals of concern.

Conclusions of evidence from this head-to-head trial programme are replicated in a series of NMAs designed to compare the efficacy and safety of further biologic treatments relevant to the NHS, at the end of treatment induction. Across these analyses, guselkumab consistently demonstrated superiority (with respect to physician reported and patient-reported outcomes) over TNF-α inhibitors, ustekinumab and secukinumab, and comparability to the newer IL-17 treatment, ixekizumab. Safety and tolerability was comparable across treatments. It should also be noted that guselkumab provides these comparable (or superior) health benefits and safety through a reduced dosing schedule, conducted in the comfort of the patients own home.

B.3.13. Ongoing studies

All studies described in this submission are ongoing and will provide additional evidence of the longer-term benefit of guselkumab in the next 12 months.

A head-to-head Phase III study designed to evaluate the comparative efficacy of guselkumab and secukinumab for the treatment of moderate to severe plaque-type psoriasis (ECLIPSE) is currently recruiting (NCT03090100).

Following positive results from a Phase II study evaluating the efficacy and safety of guselkumab for the treatment of active PsA[69], two Phase III studies in this associated indication are also currently recruiting (NCT03158285 & NCT03162796).

B.4. Cost-comparison analysis

B.4.1. Changes in service provision and management

Guselkumab is not anticipated to require any changes to current service provision and management.

Administration

Guselkumab is administered via subcutaneous (SC) injection at Weeks 0 and 4, and every 8 weeks thereafter.[16] Patients may self-inject at home if a physician determines that this is appropriate. This provision is similar to biological therapy with adalimumab, etanercept, ixekizumab, secukinumab and ustekinumab, which have all been recommended by NICE for consideration in the treatment of moderate to severe plaque psoriasis.[6, 8-11]

Moreover, Janssen funds a homecare service (Table 2) such that guselkumab is anticipated to be administered free of charge to the NHS (see B.4.2).

In addition to the recommended subcutaneous treatments for moderate to severe plaque psoriasis, NICE also recommends infliximab, which is administered intravenously in secondary care. Consequently, guselkumab constitutes a lower resource burden compared with infliximab.

Monitoring

As is the case with other biologic therapies, guselkumab requires monitoring for tuberculosis, but has no additional monitoring above that carried out currently for SC therapies recommended for use in moderate to severe psoriasis.

B.4.2. Cost-comparison analysis inputs and assumptions

Features of the cost-comparison analysis

1. Overview

A simple cost comparison was carried out to evaluate the cost to the NHS associated with the use of guselkumab versus adalimumab and ustekinumab in the treatment of adults with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated.

[redacted]).

Costs are assessed over five years, with drug costs accrued each week. A 5-year time horizon is considered appropriate to capture materially important differences between drug costs associated with guselkumab, adalimumab and ustekinumab which has been estimated based on the 20% discontinuation rate of biologics that have been previously accepted by NICE; however, alternative time horizons (one year and 10 years) are explored in sensitivity analysis (see Section B.4.4).

Costs are not discounted in the base case. This is in line with the user guide for cost comparison for fast track appraisal (FTA).[70] The impact of discounting at 3.5% is explored in sensitivity analysis (see Section B.4.4).

The simple framework for the accrual of costs is detailed below.

Adults with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated, begin treatment with either guselkumab, adalimumab or ustekinumab.

Treatment with either guselkumab, adalimumab or ustekinumab requires an initial period of treatment prior to assessment of response. During this period, we assume that all patients remain on therapy. This assumption is in line with previous appraisals for biologic treatments in moderate to severe plaque psoriasis.[71, 72]

The period of initial treatment prior to assessment of response for guselkumab adalimumab and ustekinumab is 16 weeks.[16, 71] Patients who have not responded adequately to treatment at 16 weeks are assumed to immediately discontinue therapy; patients who have responded adequately to treatment continue therapy.

The probability of responding to treatment at 16 weeks is [redacted] This value equates to the probability of achieving a response of PASI 75 for patients receiving guselkumab, based upon the results of the best-fitting adjusted network meta-analysis (NMA) (see Section B.3.9). PASI 75 was selected as the most appropriate measure of response given its wide use in clinical practice, and its use as the key measure of response in previous NICE technology appraisals (see Section B.2.1).

The probability of response is applied to both guselkumab and ustekinumab, given the assumption that guselkumab and ustekinumab are similarly efficacious. We note that, in practice, this assumption may over-estimate the efficacy associated with ustekinumab, given the NMA results described in Section B.3.9.

Patients who discontinue treatment upon assessment of response (16.52%) incur no further cost within the model. In practice, upon failure of first-line biological therapy, patients will likely receive an alternative biologic treatment at second line. However, given that the response rates for guselkumab and ustekinumab are assumed to be identical for this cost comparison, it follows that future costs of alternative biological therapies will also be identical. Therefore, we have excluded any further costs associated with subsequent treatment from the base case cost comparison. For completeness, in sensitivity analysis, we include the costs associated with a further line of therapy, best supportive care, for patients who discontinue first-line biologic treatment (see Section B.4.4).

Patients who continue treatment upon assessment of response ([redacted] continue to receive either guselkumab or ustekinumab, and incur a weekly cost associated with each therapy, estimated based upon the relevant dosing schedule and cost per item.

Patients who continue biologic treatment with guselkumab or ustekinumab have a probability of discontinuing treatment each week. In the base case, the probability of discontinuing treatment is set at an annual probability of 20%. This value was used in the absence of long-term comparative discontinuation data between ustekinumab and guselkumab. We note that this figure has previously been considered acceptable during NICE Committee deliberations and has been used in all previous appraisals relating to biological therapies for psoriasis (see Section B.2.1). An annual probability of 20% discontinuation equates to a weekly probability of discontinuing treatment of 0.43% based upon the following equation:

$$\left(1 - e^{\left(\ln(1-0.2)\times\frac{7}{365.25}\right)}\right) = 0.43\%$$

For completeness, an alternative probability of discontinuation is explored in sensitivity analysis (see Section B.4.4).

Mortality is not considered within the analysis. This is because the model time horizon is relatively short, and mortality is not expected to differ for patients receiving guselkumab versus ustekinumab.

2. Rationale for selected comparator

NICE verbally advised during the Decision Problem Meeting that it would be appropriate to compare against one biologic treatment after having established similar or better efficacy and the selection of a comparator for the cost comparison should be based upon two key considerations:

- The comparator should have a significant proportion of market share;
- The comparator should broadly represent the full group of options in terms of cost and effectiveness.

Given these considerations, we believe that ustekinumab is an appropriate comparator for this cost comparison, the full reasons for which are detailed below.

a) Market share

To ascertain market share of currently prescribed biologic treatments in the UK for the treatment of psoriasis, data from Quintiles IMS survey were used. Quintiles IMS conducts a quarterly survey of 40 dermatologist prescribers of biological therapies. The survey is anonymous, double-blinded and an independent representation of the UK market. Dermatologists were asked questions about their patients and their prescribing patterns to be answered using patient records (data on file – available upon request). The most recently available market share data from this survey are for June 2017 (Figure 17), with data from August 2014 to June 2017 summarised in Figure 18.

Figure 17: Total biologic market share June 2017 – results from a survey of 40 dermatologists and 239 patients prescribing for psoriasis

Key: Cosentyx, secukinumab; Enbrel, etanercept; Humira, adalimumab; Remicade, infliximab; Stelara, ustekinumab; Taltz, ixekizumab.

Figure 18: Total biologic market share – results from a survey of 40 dermatologists prescribing for psoriasis

Key: Cosentyx, secukinumab; Enbrel, etanercept; Humira, adalimumab; Remicade, infliximab; Stelara, ustekinumab; Taltz, ixekizumab.

Ustekinumab (Stelara) constitutes the most widely prescribed biologic treatment for psoriasis, according to the survey data. Specifically, ustekinumab comprised treatment for [redacted] of the [redacted] patients represented by the survey data collected in June 2017 (Figure 17), the largest single proportion of biological prescribing. Moreover, Figure 18 demonstrates that adalimumab and ustekinumab prescribing have been stable, with data from August 2014 to June 2017 showing ustekinumab market share steady at approximately [redacted]. We believe that this consistency and volume indicates that ustekinumab is a market leader in UK biological prescribing for psoriasis, and therefore constitutes a significant proportion of prescribing.

Adalimumab (Humira) is currently the second most widely prescribed biologic therapy with [redacted] of the patients and historically has been the market leader in

psoriasis with market share reaching up to [redacted] of the market. Together, adalimumab and ustekinumab comprised approximately [redacted] of UK prescribing in June 2017 (Figure 17 and Figure 18).

b) Comparator should broadly represent the full group of options

Ustekinumab and adalimumab are broadly representative of the full group of relevant treatment comparators outlined in the NICE scope in terms of both expected cost and expected benefit.

Table 22 outlines the expected cost as per the list price and SmPC dosing for the biological therapies included within the NICE scope for this appraisal. The unit costs used to inform these figures are provided in Appendix I.

Table 22: Cost per course, per person – NICE approved biological therapies

Therapy	Dosing	1st year cost (including induction)	Annual maintenance cost, year 2 onwards
Adalimumab	Induction: 80mg Week 0 Maintenance: 40mg every 2 weeks	£9,684	£9,156
Etanercept	Induction: 100mg per week, Week 0 to Week 12 Maintenance: 50mg per week	£9,295	£9,295
Etanercept biosimilar		£8,528	£8,528
Infliximab	Induction: 5mg/kg Week 0, Week 2, Week 6 Maintenance: 5mg/kg every 8 weeks	£11,382	£9,546
Infliximab biosimilar		£10,226	£8,577
Ixekizumab	Induction: 160mg Week 0, 80mg Week 2, 4, 6, 8, 10, 12 Maintenance: 80mg every 4 weeks	£19,125	£14,625
Secukinumab	Induction: 300mg Weeks 0, 1, 2, 3 and 4 Maintenance: monthly 300mg	£18,282	£14,625
Ustekinumab	Induction: 45mg or 90mg at Week 0 and 4 Maintenance: 45mg or 90mg every 12 weeks	£10,735	£9,304

Ustekinumab represents one of the least costly therapies in terms of both induction and maintenance, at list price (Table 22), while adalimumab is the least costly therapy at list price.

In terms of effectiveness, ustekinumab is broadly representative of the full group of therapies, and is neither the least nor most effective biologic treatment according to the NMA analyses carried out and described in Section B.3.9. Guselkumab is demonstrably superior, in terms of efficacy, to adalimumab based on head-to-head trials.

Intervention and comparators' acquisition costs

A summary of the acquisition costs analysed for guselkumab, adalimumab and ustekinumab are included in Table 23 and described below.

Table 23: Acquisition costs of the intervention and comparator technologies

	Guselkumab	Adalimumab	Ustekinumab
Pharmaceutical formulation	100mg solution for subcutaneous injection in a pre-filled syringe (1mL).	40mg solution for subcutaneous injection in a pre-filled syringe or pen.	45mg and 90mg solution for subcutaneous injection in a pre-filled syringe or vial.
(Anticipated) care setting	Primary care		
Acquisition cost (excluding VAT)	Price with PAS: [redacted] for one 100mg syringe	One pack of two 40mg doses: £704.28	One 45mg syringe: £2,147 One 90mg syringe: £2,147
Method of administration	Subcutaneous injection		
Doses	100mg dose per injection	80mg induction (week 0); thereafter 40mg	For patients with body weight ≤100kg, 45mg dose per injection For patients >100kg, 90mg dose per injection
Dosing frequency	Guselkumab is administered in Week 0, Week 4, and thereafter every 8 weeks	At induction and thereafter every 2 weeks	Ustekinumab is administered in Week 0, Week 4, and thereafter every 12 weeks
Dose adjustments	NA		

	Guselkumab	Adalimumab	Ustekinumab
Average length of a course of treatment	Average time on treatment: 2.74 years over a 5-year time horizon		
Average cost of a course of treatment (acquisition costs only)	[redacted]	£25,785	£27,928
Average interval between courses of treatment	N/A – continuous treatment		
Number of repeat courses of treatment	N/A		
Key: N/A, not applicable; PAS, patient access scheme; VAT: value-added tax.			

Each of guselkumab, adalimumab and ustekinumab are administered subcutaneously, and are available as pre-filled syringes. Guselkumab is administered at Week 0, 4, and thereafter every 8 weeks at a dose of 100mg per administration. For guselkumab, consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment.[16] Guselkumab is available in a 100mg dose; therefore, the cost associated with vial wastage is not considered within this analysis.

Adalimumab is administered at Week 0, and thereafter every two weeks at doses of 80mg and 40mg respectively. Ustekinumab is administered at Week 0, 4, and thereafter every 12 weeks at a dose of either 45mg or 90mg per administration. Patients with a body weight below or equal to 100kg receive the 45mg dose, with patients weighing more than 100kg receiving the 90mg dose. Ustekinumab is available in a 45mg and 90mg dose, and the two doses are priced identically.

As with guselkumab, given that the required doses of adalimumab and ustekinumab match the available formulations, vial wastage is not considered within this analysis.

The average length of a course of treatment and the associated average cost of treatment are estimated using results from the cost-comparison analysis over a 5-year time horizon. The average time on treatment was estimated to be 2.74 years for

both guselkumab and ustekinumab based upon assumptions made for efficacy and discontinuations; the average time on treatment was identical for both treatments. The average drug acquisition cost over 5 years for guselkumab, adalimumab, and ustekinumab was estimated to be [redacted], £25,785 and £27,928, respectively. [redacted] the cost comparison takes no account of cost benefits that may arise from guselkumab's greater efficacy as demonstrated in the head-to-head trials. Intervention and comparators' healthcare resource use and associated costs are expected to be similar among biologic subcutaneous biologic therapies and therefore have been excluded in these analyses.

[redacted]

1. *Administration*

Guselkumab, adalimumab, and ustekinumab are administered via SC injection. Patients are likely to self-inject following an initial period of training, if a physician determines that this is appropriate; this is consistent with the administration modelled by the manufacturer for TA442[72], the ERG for which considered the approach taken as consistent with previous assessments and adequate for the decision problem.[11]

Janssen funds a homecare service, through which the SC injection is administered to patients at home, either by self-injection following nurse training visits over the course of the first 2–3 doses, or by an ongoing nurse administration service for patients who are not suitable for self-injection.

[redacted]

2. *Monitoring*

Guselkumab requires no additional monitoring above that carried out currently for subcutaneously administered therapies recommended for use in moderate to severe psoriasis. [redacted]

[redacted]

Adverse reaction unit costs and resource use

As reported in Section B.3.9, results of the NMA analyses for AEs indicate that the incidence of AEs associated with the use of guselkumab, adalimumab, and ustekinumab are similar.

Given the similarity in adverse event incidence, we assume that the cost associated with treating adverse events would be similar for all therapies, and therefore that any difference in cost caused by adverse events associated with guselkumab would be negligible. Consequently, we omit these costs from the analysis.

We note that this approach is consistent with the approach taken in previous, relevant NICE technology appraisals (Section B.2.1).

Miscellaneous unit costs and resource use

[redacted]

Uncertainties in the inputs and assumptions

Inputs used in the base case cost comparison are summarised in Table 24. The key assumptions of the cost-comparison analysis are summarised in Table 25.

Table 24: Summary of model inputs

Input	Base case value	Reference
Time horizon (years)	5.00	NICE FTA user guide[70]
Discount rate	0.00%	NICE FTA user guide[70]
Time until initial response assessment, guselkumab (weeks)	16	Draft SmPC for guselkumab[16]
Time until initial response assessment, ustekinumab (weeks)	16	NICE TA180[71]
Pack cost of guselkumab (1x100mg)	[redacted]	Janssen
Pack cost of adalimumab (2x40mg)	704.28	eMIMS[73]

Input	Base case value	Reference
Pack cost of ustekinumab (Stelara) (1x45mg)	£2,147	eMIMS[73]
Pack cost of ustekinumab (Stelara) (1x90mg)	£2,147	eMIMS[73]
Dosing schedule for guselkumab	100mg dose per injection administered in Week 0, Week 4, and thereafter every 8 weeks	Draft SmPC for guselkumab[16]
Dosing schedule for adalimumab	80mg induction (week 0); thereafter 40mg every 2 weeks	SmPC for adalimumab[74]
Dosing schedule for ustekinumab	For patients with body weight ≤100kg, 45mg dose per injection. For patients >100kg, 90mg dose per injection. Administered in Week 0, Week 4, and thereafter every 12 weeks	SmPC for ustekinumab[75]
[redacted]	[redacted]	NMA analyses (Section B.3.9)
Probability of discontinuation (guselkumab, adalimumab and ustekinumab)	20% annually	NICE TA442 and TA475[13, 72]
Key: FTA, fast-track appraisal; MIMS, Monthly Index of Medical Specialties; NMA, network meta-analysis; SmPC, summary of product characteristics; TA, technology appraisal.		

Table 25: Key assumptions of the analysis

Assumption	Rationale for assumption	Relevant sensitivity analysis
Adalimumab and ustekinumab are appropriate comparators	Adalimumab and ustekinumab comprise a similar roportion of market share associated with biologic treatments for psoriasis. Their cost and effectiveness is considered representative of other comparator therapies.	N/A
Patients are assumed to remain on initial biologic treatment until assessment of response	This assumption is aligned with published NICE technology appraisals for moderate to severe plaque psoriasis, including TA442 and the FAD for TA475.[13, 72]	N/A
Response to treatment with adalimumab and ustekinumab is assessed at 16 weeks	Based upon the stopping rule described in NICE TA146 for adalimumab and NICE TA180 for ustekinumab, treatment should be stopped in people whose	N/A

Assumption	Rationale for assumption	Relevant sensitivity analysis
	psoriasis has not responded adequately by 16 weeks after starting treatment.[8, 71]	
Response to treatment with guselkumab is assessed at 16 weeks	Based upon the draft SmPC for guselkumab: "For guselkumab, consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment"[16]	N/A
The probability of responding to treatment is assumed to be identical for ustekinumab, adalimumab and guselkumab	Given the results of the NMA analyses for PASI 75, guselkumab is associated with a similar or better relative efficacy compared with adalimumab and ustekinumab.	N/A
The annual probability of discontinuation after the initial assessment of response is 20% for each of guselkumab, adalimumab, and ustekinumab	This value was used in the absence of long-term comparative discontinuation data between adalimumab, ustekinumab and guselkumab, and is aligned with published NICE technology appraisals for moderate to severe plaque psoriasis, including TA 442 and TA475.[13, 72]	A sensitivity analysis is carried out in which discontinuation data from alternative sources are explored (Section B.4.4)
Adverse events are equivalent between guselkumab adalimumab, and ustekinumab	NMA data for adverse events indicate that adverse event incidence for patients treated with either guselkumab, adalimumab, and ustekinumab are similar. Consequently, we omit these costs from the analysis.	N/A
[redacted]	[redacted]	N/A
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]

Assumption	Rationale for assumption	Relevant sensitivity analysis
Mortality is not included in the model	The time horizon is short, and mortality is not expected to differ by therapy.	N/A
Vial wastage is not considered within the analysis	Guselkumab, adalimumab and ustekinumab are available in the size of formulation that is appropriate for administration. Consequently, vial sharing is not possible, and estimates of vial wastage are not necessary.	N/A
Key: FAD, final appraisal determination; N/A, not applicable; NMA, network meta-analysis; PASI, psoriasis area and severity index; SmPC, summary of product characteristics; TA, technology appraisal.		

B.4.3. Base-case results

Guselkumab can be considered a cost-effective option for the treatment of moderate to severe plaque psoriasis compared to adalimumab and ustekinumab [redacted] (see Sections B.3.6 and B.3.9). The total per-person drug acquisition cost for guselkumab adalimumab, and ustekinumab was estimated to be [redacted], £25,785 and £27,928, respectively, over the 5-year time horizon (Table 26). Though this equates to [redacted] over five years in the case of guselkumab compared with adalimumab, guselkumab is clearly superior to adalimumab in terms of efficacy, as demonstrated in the head-to-head evidence. Guselkumab is [redacted] per person over five years when compared with ustekinumab. Overall, guselkumab demonstrates excellent value to the NHS.

Table 26: Base-case results; 5-year time horizon

Technologies	Acquisition costs	Resource costs	Adverse event costs	Total cost
Guselkumab	[redacted]	N/A	N/A	[redacted]
Guselkumab compared to adalimumab:				
Adalimumab	£25,785	N/A	N/A	£25,785
Difference	[redacted]	N/A	N/A	[redacted]
Guselkumab compared to ustekinumab:				
Ustekinumab	£27,928	N/A	N/A	£27,928,
Difference	[redacted]	N/A	N/A	[redacted]
Key: N/A, not applicable				

B.4.4. Sensitivity and scenario analyses

One-way sensitivity analysis (OWSA) was carried out on the results, varying the relevant inputs between upper and lower values.

- Time until initial response assessment was varied ±20%
- Probability of initial response at the end of induction period (all therapies)
- The time horizon was varied between 1 and 10 years.
- The discontinuation rate was set at a minimum 8.6% (as per Menter et al.[47]) and maximum 24% (base case plus 20%)
- The discount rate was varied between 0% and 3.5%.

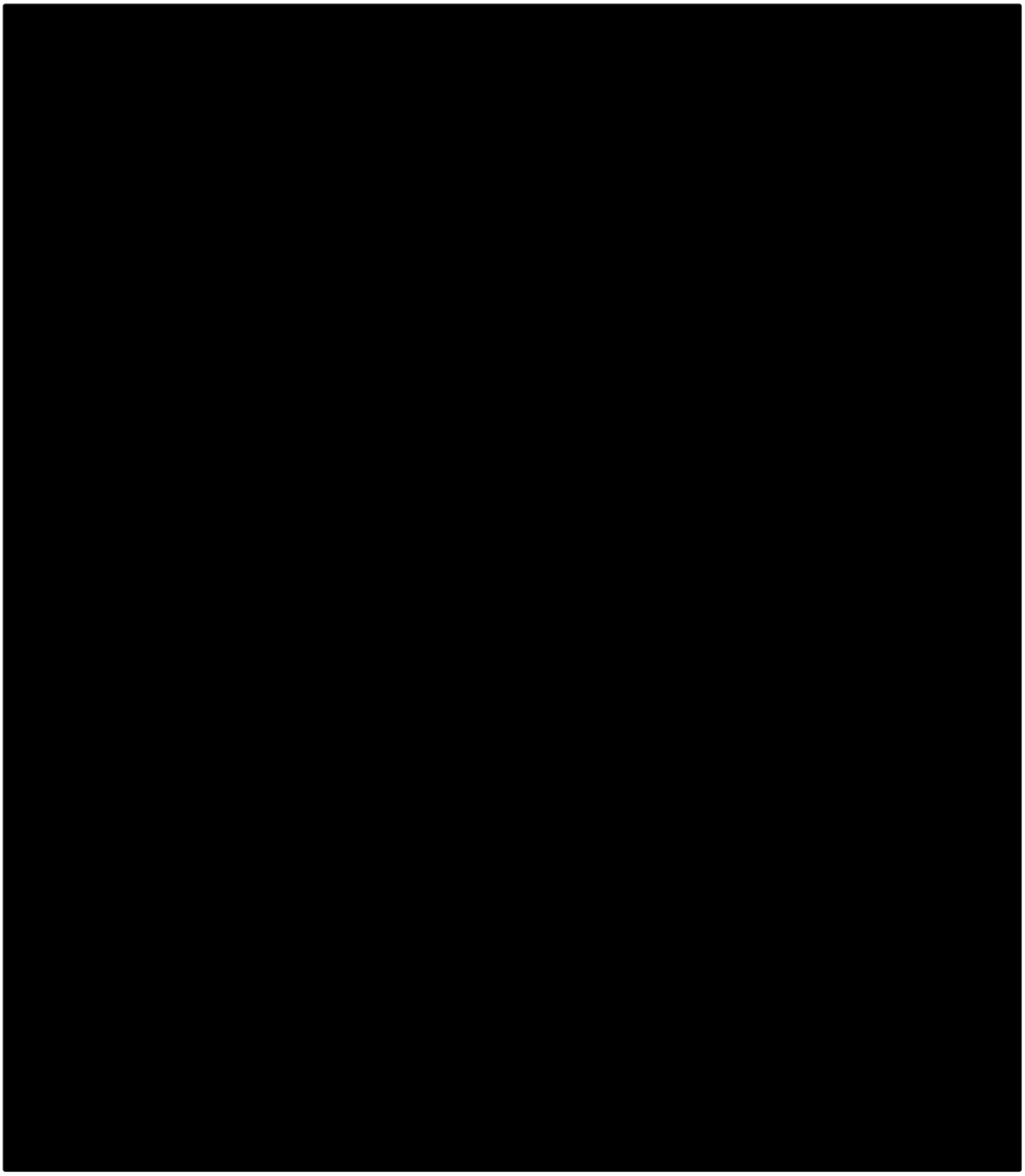
The results of the OWSA are presented in Table 27 and Figure 19.

Table 27: Results of the one-way sensitivity analysis (difference in total cost)

		Adalimumab		Ustekinumab	
Most influential variables		**(low value)**	**(high value)**	**(low value)**	**(high value)**
Time until initial response assessment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probability of initial response*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual probability discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate (% per annum)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- For both comparisons the analysis was most sensitive to assumptions as to time of initial response assessment and the time horizon, both of which impact on total acquisition costs and therefore cost differences. Reducing the probability of discontinuation resulted in increased costs for all therapies; however, these increases had little impact on the incremental cost associated with use of guselkumab, [redacted]

Figure 19: Results of the one-way sensitivity analysis



B.4.5. Subgroup analysis

No subgroup analyses were considered as part of the cost comparison.

B.4.6. Interpretation and conclusions of economic evidence

The present cost comparison shows that guselkumab has [redacted] to adalimumab and has demonstrated clear superiority in terms of efficacy in head-to-head clinical trials. In addition, guselkumab is [redacted] versus ustekinumab and the NMA has demonstrated better efficacy.

Adalimumab and ustekinumab were selected as comparators due to their significant market shares. Adalimumab currently has [redacted] market share, and ustekinumab is the current market leader at [redacted] and thus we felt that both comparators were of relevance to the decision problem. In addition, it is important to note that any uncertainties that may arise through the NMA are negated by the strong head to head Phase III clinical trial evidence demonstrating clear superiority of guselkumab over adalimumab, and of patients who had crossed over to guselkumab once they had failed ustekinumab.

Costs associated with administration, monitoring, and adverse events were excluded from the analysis, because guselkumab is not associated with any additional burden versus either comparator. In addition, costs of future lines of therapy were omitted from the analysis given that efficacy was assumed to be identical across therapies, and therefore, costs of future lines of therapy would also be identical.

We consider that the results of the base case and sensitivity analyses are robust, and that guselkumab represents clear value for money for the NHS in the treatment of adults with moderate to severe plaque psoriasis for whom non-biologic systemic treatment or phototherapy is inadequately effective, not tolerated or contraindicated.

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B.6. Appendices

Appendix C: Summary of product characteristics and European public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Checklist of confidential information

Appendix I: Unit costs of biological therapies

Appendix J: Description of included scenario analyses

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Single technology appraisal

Guselkumab for treating moderate to severe plaque psoriasis [ID1075]

Dear Company,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 25 October from Janssen. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

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

Please provide your written response to the clarification questions by the end of **27 November**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

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

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

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

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

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

Yours sincerely

Jasdeep Hayre
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **PRIORITY QUESTION**: What was the discontinuation rate for guselkumab in VOYAGE 1, including the extension phase? If possible, please provide:

a) a breakdown of the reasons for discontinuation.

b) discontinuation rates for the comparators (adalimumab and ustekinumab).

A2. **PRIORITY QUESTION**: NAVIGATE trial: please provide evidence that the ustekinumab patients randomised to continue ustekinumab received sufficient dosage to allow an unbiased comparison with guselkumab at 40 weeks.

A3. **PRIORITY QUESTION**: Approximately 20% of patients in the VOYAGE trials had previously received biological(s). Please comment on the significance of this for the decision problem. In particular, please clarify the possible impact on PASI75 and PASI90 outcome measures.

A4. **PRIORITY QUESTION**: In the VOYAGE trials, it appears that about 40% of patients on biological treatment had not previously received phototherapy or non-biological systemic treatment. Please comment on the likely impact that this might have on PASI75 and PASI90 outcome measures.

A5. **PRIORITY QUESTION**: How different were centres and investigators between VOYAGE 1 and 2 and NAVIGATE?

A6. **PRIORITY QUESTION**: To support consistency in the network meta-analyses, the company conducted pairwise conventional meta-analyses of PASI response for guselkumab compared with placebo and adalimumab, using the guselkumab trials (NMAs) (company submission section B.3.8 and appendix D figures 58–61). Please provide corresponding analyses using available evidence for other drugs included in the NMA networks, but especially for the chosen comparators (adalimumab and ustekinumab).

A7. **PRIORITY QUESTION**: The following priority questions relate to the NMA:

a) Please reproduce the NMA using change of DLQI score as the outcome

b) Please provide results of tests comparing inconsistency and consistency models, namely the DIC for the inconsistency models.

c) The ERG has concerns about the difference in evidence networks between the ‘full’ network and the ‘restricted’ network (described in the company submission as the decision comparator set or focussed network [page 74 document B]). It

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appears that the company prioritised the broader evidence networks, which contradicts the company view on the treatment pathway (figure 1 company submission), namely that guselkumab would be used after treatments that were included in the full network (for example, apremilast).

i. It appears that the "full network" is presented in Appendix D, please confirm that this is correct.

ii. Please provide the study-inclusion criteria and network diagrams for the 'restricted networks' / 'focussed networks' / 'sensitivity analysis'

iii. Please also confirm that the decision comparator set NMA should be considered as the primary NMA for this submission.

d) Please clearly define the different NMAs presented in terms of treatments included (for example, Decision comparator set [13-14 treatments], full network [19 treatments]).

e) ABP 501 (adalimumab biosimilar) appears in Figure 13 of Document B of the company submission, but not Figure 12. Please update NMA results as necessary.

f) Please produce an unadjusted NMA for the decision problem.

g) Please reproduce the NMA and pairwise comparisons on safety including the safety from 'as-treated' population of NAVIGATE.

h) Please produce an NMA adjusted for both baseline risk and duration of psoriasis.

i) Please produce a safety NMA for the decision comparator set (focused network), like in Figures 21–23 of Appendix D. Please provide unadjusted results and results adjusted for baseline risk.

j) How were the covariates included in the models: as mean-centred or centred otherwise? Please clarify whether the meta-regression models were parametrised as having a common effect against all treatment-placebo comparisons, or had an exchangeable or unrelated effect.

A8. **PRIORITY QUESTION**: Please reproduce Table 19 in Document B of the company submission including the ustekinumab arms of the trial and the 95% confidence intervals.

A9. **PRIORITY QUESTION**: Please outline the arithmetic used to derive the following outcomes for placebo, guselkumab, ustekinumab and adalimumab from the central estimates in Table 14 of Document B: PASI75, PASI90, PASI100, DLQI 0/1 and SAEs. This can be supplied in an excel spreadsheet.

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A10. Blinding in the VOYAGE and NAVIGATE trials appears to be achieved by giving placebo injections during gaps between dosing times for the adalimumab, guselkumab and ustekinumab regimens. Were similar methods used in other head-to-head and placebo-controlled trials of anti-IL and anti-TNF agents?

A11. Suicide and suicide ideation appear to be concerns with anti-IL agent treatment. In the trials of guselkumab, patients receiving lithium were excluded. Might this result in an underestimation of the suicide risk?

A12. In the schematic overview of the NAVIGATE trial (Figure 4 of Document B of the company submission), the active treatment phase begins at week 16 and ends at week 44. However, the results (Table 13 of Document B) present a different timeline (weeks 28 to 40). Please clarify.

A13. Please provide data for the proportion of LOCF used in the PASI90 and PASI75 graphs from VOYAGE 1 and its extension.

A14. The text in Document B of the company submission states that "Apremilast and DMF are small molecule, non-biologic, oral treatments with significantly lower degrees of efficacy and differing safety profiles to the biologic therapies and would only be considered for use in patients unsuitable for biologic treatment or unwilling to receive biologic treatment". Figure 1 of Document B of the company submission suggests that patients would only use apremilast or DMF before biologics. Please clarify.

A15. Please provide the equivalent of Figure 13 in Document B of the company submission for:

- PASI100 at the end of induction analysis (2 figures: one with adjusted and one with unadjusted results)
- SAEs (2 figures: adjusted and unadjusted).

A16. Please provide the equivalent of Table 14 and Figures 12, 13, 14 and 16 of Document B for an analysis which does not adjust for covariates.

Section B: Clarification on cost-comparison analysis

B1. **PRIORITY QUESTION**: Please provide the England and Wales market share data (n patients, or if n patients is not available % market share) for ixekizumab, secukinumab, ustekinumab, infliximab, adalimumab, etanercept and other drug treatments separately for each of the past 36 months (in one table, see below), also stating the date that the latest full month market share data relates to. If monthly quantities are not available, please provide the most disaggregate format that is; e.g., quarterly, including the Jul-Sep 2017 quarter.

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- Please outline whether this market share data is specific to people with severe plaque psoriasis (as defined in the NICE technology appraisal recommendations for biologics), moderate to severe plaque psoriasis, plaque psoriasis or a wider patient group. Was it specific to people who were intolerant or contraindicated to, or whose psoriasis had not responded to, standard systemic therapies (ciclosporin, methotrexate and PUVA)?
- How were the 40 dermatologists selected for the market share analysis?
- Are the psoriasis patients reported by the company restricted to only NHS patients?
- What makes these patients representative of NHS practice as a whole?

This information can be supplied within an excel spreadsheet if this is simpler.

Month to date	Oct 2017	Sep 2017	Etc…
Ixekizumab	n=???	n=???	n=???
Secukinumab	n=???	n=???	n=???
Ustekinumab	n=???	n=???	n=???
Infliximab	n=???	n=???	n=???
Adalimumab	n=???	n=???	n=???
Etanercept	n=???	n=???	n=???
Other (pooled)	n=???	n=???	n=???

B2. **PRIORITY QUESTION**: The analysis includes a response assessment at week 16, to determine whether the treatment stops or continues. Do the costings for adalimumab assume that response is assessed before or after the week 16 dose has been administered? That is, do all patients receive 1*80mg dose and 7*40mg doses or 8*40mg doses?

B3. **PRIORITY QUESTION**: Please tabulate the input values that are changed from the base case for the sensitivity analysis “Probability of initial response at the end of induction period (all therapies)”. Please provide the rationale for the values used in this sensitivity analysis.

B4. **PRIORITY QUESTION**: Janssen funds a homecare service for those who cannot self-inject.

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a. Please provide more detail of what this funds, the annual funding per patient or per patient visit, whether this is NHS or private sector nurses and how this funding is arranged.

b. What proportion of people with plaque psoriasis receiving ustekinumab in the UK require this service? If this cannot be provided specific to people with plaque psoriasis, please provide it for the smallest patient group that encompasses these patients.

c. If Janssen is aware of any comparator companies providing a similar self-injection service, please provide details of these.

B5. The company's assumption of a 20% discontinuation rate for all 3 treatments in its cost comparison analysis does not reflect real world discontinuation rates reported by Arnold et al. (2016), Menter (2016), Warren (2015). These suggest higher discontinuation for adalimumab (~20%/year) than for ustekinumab (~8%/year). Please explain how using different annual withdrawal rates for each comparator might alter the results of the cost-comparison, and how this might interplay with treatment sequence?

Section C: Textual clarifications and additional points

C1. There appears to be a typo about NAVIGATE on pages 163-4 of the appendices. Current statement: "Patients who responded to initial ustekinumab therapy were randomised to receive either guselkumab or ustekinumab". Please confirm that this should read: "Patients who didn't respond to initial ustekinumab therapy were randomised to receive either guselkumab or ustekinumab".

C2. Mortality as an outcome is not addressed in this submission. Please update Table 1 ("Decision Problem") in Document B of the company submission accordingly.

C3. Please confirm the duration of induction with guselkumab and when the first maintenance dose is administered. Table 7 of the appendix state that the induction period in the VOYAGE trials was 16 weeks, however some descriptions of the dosing schedule imply that the first maintenance dose is administered at week 12. Please clarify.

C4. Pages 102–3 of the company submission refer to only ustekinumab as a comparator. Please confirm that adalimumab should have been included in these statements.

Section D. References

Arnold T, Schaarschmidt ML, Herr R, Fischer JE, Goerdt S, Peitsch WK. Drug survival rates and reasons for drug discontinuation in psoriasis. J Dtsch Dermatol Ges. 2016;14(11):1089-1099.

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Iskandar IYK, Warren RB, Lunt M, Mason KJ, Evans I, McElhone K, Smith CH, Reynolds NJ, Ashcroft DM, Griffiths CEM; BADBIR Study Group. Differential drug survival of second-line biologic therapies in patients with psoriasis: Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2017 Oct 25. pii: S0022-202X(17)33068-3.

Menter A, Papp KA, Gooderham M, Pariser DM, Augustin M, Kerdel FA, Fakharzadeh S, Goyal K, Calabro S, Langholff W, Chavers S, Naessens D, Sermon J, Krueger GG. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Eur Acad Dermatol Venereol. 2016; 30(7):1148-58.

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Single technology appraisal

Guselkumab for treating moderate to severe plaque psoriasis [ID1075]

Dear Company,

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have looked at the submission received on 25 October from Janssen. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

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

Please provide your written response to the clarification questions by the end of **27 November**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

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

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

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

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

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

Yours sincerely

Jasdeep Hayre
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **PRIORITY QUESTION**: What was the discontinuation rate for guselkumab in VOYAGE 1, including the extension phase? If possible, please provide:

a) a breakdown of the reasons for discontinuation.

b) discontinuation rates for the comparators (adalimumab and ustekinumab).

Discontinuation rates for guselkumab in VOYAGE 1, VOYAGE 2 and NAVIGATE, and a breakdown of the reasons for discontinuation are provided in Table 1.

Discontinuation rates for the comparators in VOYAGE 1, VOYAGE 2 and NAVIGATE, and a breakdown of the reasons for discontinuation are provided in Table 2.

Data are provided for the active treatment period of the NAVIGATE trial (Week 16 to Week 44) as patient withdrawals in the follow-up phase were not treatment discontinuations, rather study terminations. In total, 41 patients (15.3% of all randomised patients) terminated study participation prior to Week 60 with the most common reason being patient withdrawal (10.1%).

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Table 1: Patients who discontinued guselkumab

	VOYAGE 1					VOYAGE 2			NAVIGATE
	Week 0-48		Week 0-100			Week 0-48			Week 16-44
	PBO-GUS[a]	GUS	PBO-GUS[a]	GUS	ADA-GUS[b]	PBO-GUS[a]	GUS	ADA-GUS[c]	GUS
Randomised, n	165	329	[redacted]	[redacted]	[redacted]	233	496	146	135
Treated, n	165	329	[redacted]	[redacted]	[redacted]	233	494	146	135
Patients who discontinued, n (%)	3 (1.8)	28 (8.5)	[redacted]	[redacted]	[redacted]	14 (6.0)	39 (7.9)	3 (2.1)	9 (6.7)
Reasons for discontinuation, n (%):									
Adverse event	1 (0.6)	10 (3.0)	[redacted]	[redacted]	[redacted]	3 (1.3)	13 (2.6)	1 (0.7)	3 (2.2)
Worsening PsO	0	0				1 (0.4)	1 (0.2)	0	0
Other AE	1 (0.6)	10 (3.0)				2 (0.9)	12 (2.4)	1 (0.7)	3 (2.2)
Death	0	0	[redacted]	[redacted]	[redacted]	0	0	0	0
Lack of efficacy	0	3 (0.9)	[redacted]	[redacted]	[redacted]	0	2 (0.4)	1 (0.7)	3 (2.2)
Lost to follow-up	1 (0.6)	3 (0.9)	[redacted]	[redacted]	[redacted]	3 (1.3)	10 (2.0)	0	0
Patient choice	1 (0.6)	4 (1.2)	[redacted]	[redacted]	[redacted]	4 (1.7)	6 (1.2)	1 (0.7)	2 (1.5)
Non-compliance	0	5 (1.5)	[redacted]	[redacted]	[redacted]	1 (0.4)	1 (0.2)	0	1 (0.7)
Protocol violation	0	1 (0.3)	[redacted]	[redacted]	[redacted]	2 (0.9)	3 (0.6)	0	0
Pregnancy	0	0	[redacted]	[redacted]	[redacted]	0	2 (0.4)	0	0
Other	0	2 (0.6)	[redacted]	[redacted]	[redacted]	1 (0.4)	2 (0.4)	0	0

Key: ADA, adalimumab; AE, adverse event; GUS, guselkumab; PBO, placebo; PsO, psoriasis.
Notes: [a], includes patients who were randomised to placebo at Week 0 and cross over to receive guselkumab; [b], includes patients who were randomised to adalimumab at Week 0 and crossed over to receive guselkumab at Week 52; [c], includes patients who were randomised to adalimumab at Week 0 and crossed over to receive guselkumab at Week 24.

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Table 2: Patients who discontinued comparators (adalimumab and ustekinumab)

	VOYAGE 1		VOYAGE 2	NAVIGATE
	Week 0-48	Week 0-52	Week 0-48	Week 16-44
	ADA	ADA	ADA	UST
Randomised patients, n	334	334	248	133
Treated patients, n	333	333	248	133
Patients who discontinued, n (%)	52 (15.6)	54 (16.2)	25 (10.1)	20 (15.0)
Reasons for discontinuation, n (%):				
Adverse event Worsening PsO Other AE	11 (3.3) 5 (1.5) 6 (1.8)	13 (3.9) 5 (1.5) 8 (2.4)	8 (3.2) 2 (0.8) 6 (2.4)	2 (1.5) 0 2 (1.5)
Death	0	0	0	0
Lack of efficacy	12 (3.6)	12 (3.6)	5 (2.0)	10 (7.5)
Lost to follow-up	6 (1.8)	6 (1.8)	6 (2.4)	1 (0.8)
Patient choice	14 (4.2)	14 (4.2)	2 (0.8)	5 (3.8)
Non-compliance	4 (1.2)	4 (1.2)	2 (0.8)	0
Protocol violation	1 (0.3)	1 (0.3)	2 (0.8)	0
Pregnancy	1 (0.3)	1 (0.3)	0	0
Other	3 (0.9)	3 (0.9)	0	2 (1.5)
Key: ADA, adalimumab; AE, adverse event; PsO, psoriasis; UST, ustekinumab.				

A2. **PRIORITY QUESTION**: Please confirm that by 16 weeks in NAVIGATE "ustekinumab-non-responders" (IGA ≥2) had received two doses of ustekinumab. Also, as far as evidence allows, please assess whether the proportion of non-responders to ustekinumab in NAVIGATE (at 16 weeks) is in line with what would be expected from other ustekinumab studies identified in the "global NMA".[a]

The NAVIGATE trial provides supportive evidence on the clinical benefits of guselkumab in patients with moderate to severe plaque psoriasis, who were candidates for phototherapy or systemic treatment and who have an inadequate response to ustekinumab. Data from this trial demonstrate the benefits of the IL-23-targeted mode of action (compared with the IL-12/IL-23 mode of action for ustekinumab). Of note, the NAVIGATE trial did not meet the selection criteria for the systematic literature reviews (SLRs) described in Appendix D due to the open-label period where all patients received ustekinumab prior to randomisation.

[a] Question revised following call to discuss ERG clarification queries

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A total of 871 patients were enrolled in the NAVIGATE trial and received open-label ustekinumab 45mg or 90mg according to their baseline weight in line with standard induction dosing instructions:

"*the recommended posology of STELERA is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter*. *For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter"*[1]

At Week 16, a total of 853 patients (97.9% of all patients enrolled) remained in the study and were assessed for response using the Investigators Global Assessment (IGA) criteria: those patients with an IGA ≥2 (n=268) were considered non-responders and were subsequently randomised to continue ustekinumab (n=133) or switch to guselkumab (n=135).

A simple comparison as to whether the proportion of non-responders to ustekinumab in NAVIGATE at Week 16 (31.4%) is in line with what would be expected from other ustekinumab trials is limited due to the use of IGA to assess response, compared with a Psoriasis Area Severity Index (PASI) response assessment which is more commonly used in clinical trials, and is widely used in clinical practice.

A comparison of PASI 75 response rates has thus been conducted across the PHOENIX trials identified in the SLR used for the network meta-analysis (NMA) and the NAVIGATE trial (naïve comparison and adjusted comparison using Individualised Patient Data [IPD]); results of these analyses are presented in [redacted]. Of note, PHOENIX IPD used for analyses only included patients that were treated with ustekinumab as per label dosing.

Analyses across PASI 90 and PASI 100 response show consistent results, and a high correlation between IGA and PASI 75[2] supports the generalisability of outcomes from these analyses to assessment of response in the NAVIGATE trial. In summary, these analyses confirm that the proportion of non-responders to ustekinumab in NAVIGATE are in line with what would be expected from other ustekinumab studies.

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A3. **PRIORITY QUESTION**: Approximately 20% of patients in the VOYAGE trials had previously received biological(s). Please comment on the significance of this for the decision problem. In particular, please clarify the possible impact on PASI75 and PASI90 outcome measures.

NICE have recommended biological therapies as a treatment option for adults with plaque psoriasis when the following criteria are met:

- The disease is severe, as defined by a total PASI of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
- The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant of, or has a contraindication to, these treatments.

Patients considered suitable for biological therapy will be treated with the same biologic agent for as long as it continues to work. When their response to treatment starts to wane or they experience adverse side effects, patients will be offered a different biologic agent.

Although guselkumab is anticipated to be used in the first-line biologic setting in the majority (based on the clinical- and cost-comparison evidence presented), it may also be used in the subsequent-line biologic setting in line with this practice. Both biologic-naïve and biologic-exposed patients are therefore relevant to the decision problem and reflect the use of current biologic treatments in clinical practice.

Pre-specified subgroup analyses confirm a consistent benefit in favour of guselkumab regardless of previous exposure to biologic status and no different between the subgroups were found when compared to placebo or adalimumab. Subgroup analyses for guselkumab versus placebo at Week 16 were provided in Appendix E; subgroup analyses for guselkumab versus adalimumab at Week 24 are provided in Figure 1 and Figure 2.

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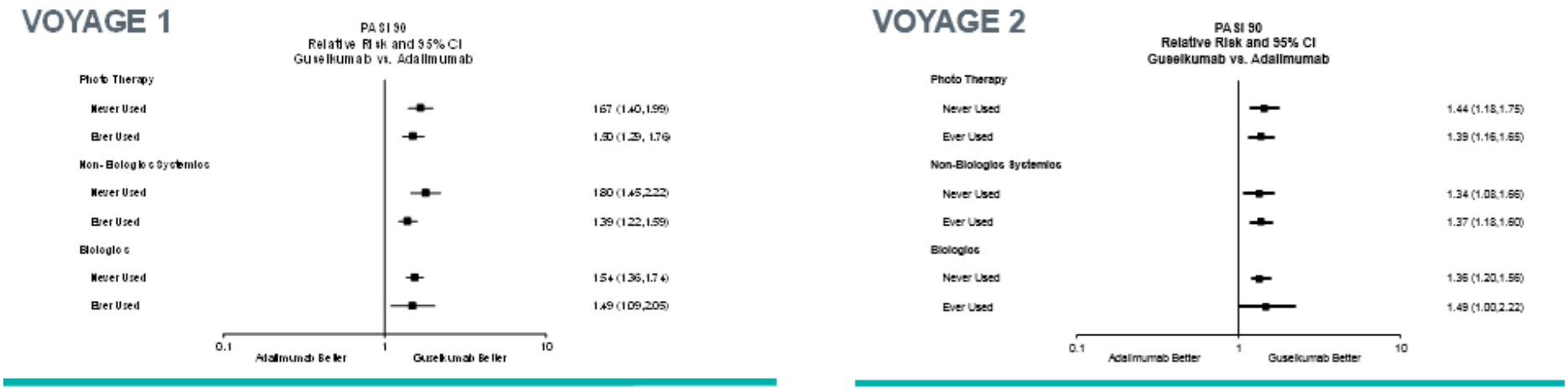
Figure 1: percent of patients randomised at Week 0 achieving PASI 90 response through Week 24; guselkumab versus adalimumab by psoriasis medication history



Key: PASI, Psoriasis Area Severity Index.

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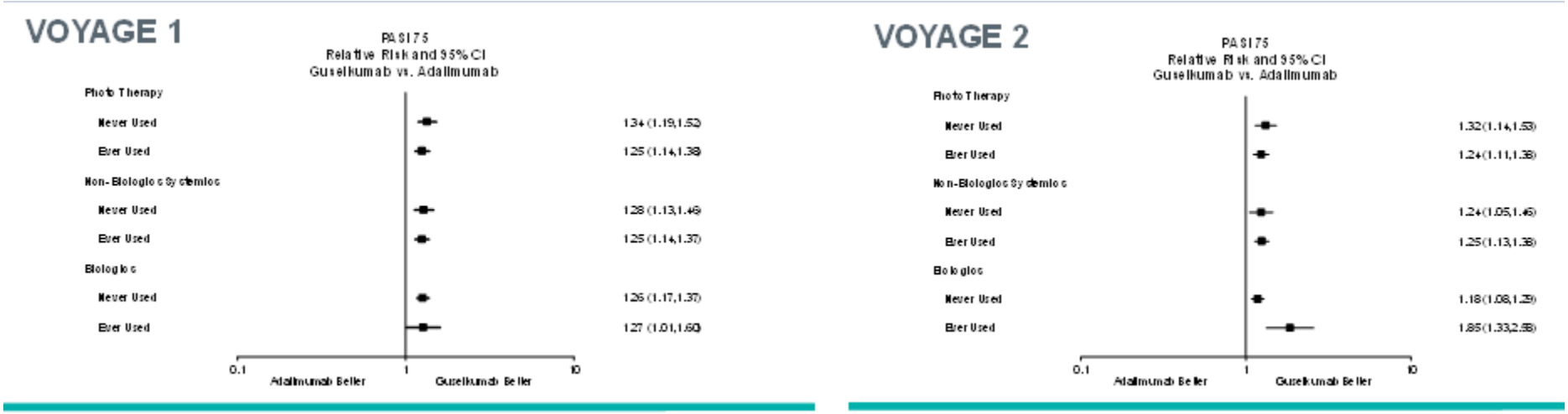
Figure 2: percent of patients randomised at Week 0 achieving PASI 75 response through Week 24; guselkumab versus adalimumab by psoriasis medication history



Key: PASI, Psoriasis Area Severity Index.

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A4. **PRIORITY QUESTION**: In the VOYAGE trials, it appears that about 40% of patients on biological treatment had not previously received phototherapy or non-biological systemic treatment. Please comment on the likely impact that this might have on PASI75 and PASI90 outcome measures.

It is acknowledged that a proportion of patients enrolled in the VOYAGE trials (37%) had not previously received phototherapy or non-biological systemic treatment, as discussed in Section B.3.11 of the company submission.

Pre-specified subgroup analyses of PASI75 and PASI90 showed no statistical differences or trends between patients who had 'never used' or 'ever used' phototherapy or non-biological systemic treatment with a consistent benefit in favour of guselkumab observed. Subgroup analyses for guselkumab versus placebo at Week 16 were provided in Appendix E; subgroup analyses for guselkumab versus adalimumab at Week 24 are provided in Figure 1 and Figure 2.

A5. **PRIORITY QUESTION**: How different were centres and investigators between VOYAGE 1 and 2 and NAVIGATE?

A summary of the geographical spread of the clinical sites across the guselkumab trials is provided in Table 3.

Table 3: Location of clinical sites enrolled in the guselkumab trial programme

	VOYAGE 1	VOYAGE 2	NAVIGATE
Total number of clinical sites	101	115	76
Number of clinical sites in:			
North America			
Canada	11	10	8
US	27	31	25
Eastern Europe			
Czech Republic	0	7	0
Hungary	6	0	0
Poland	7	18	18
Russia	12	11	5
Western Europe			
Germany	14	10	7
Spain	5	9	2

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	VOYAGE 1	VOYAGE 2	NAVIGATE
Asia Pacific			
Australia	7	6	3
South Korea	6	13	4
Taiwan	6	0	4
Notes: NAVIGATE data based on randomised patients who were enrolled across 76 sites rather than the 100 total sites involved in the trial.			

Pre-specified subgroup analyses based on demographic characteristics at baseline, including geographical location (North America vs Non-North America) and no differences based in geographic region were found in this analysis, as summarised in Appendix E accompanying Document B.

Further analyses of the primary endpoints based on the location of clinical sites, are summarised in Table 4 for the VOYAGE trials and Table 5 for the NAVIGATE trial, and further support a consistent benefit in favour of guselkumab across centres and investigators.

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Table 4: Primary endpoint analyses of VOYAGE 1 and VOYAGE 2 based on the location of clinical site

	VOYAGE 1					VOYAGE 2				
	Week 16			Week 24		Week 16			Week 24	
	PBO	GUS	ADA	GUS	ADA	PBO	GUS	ADA	GUS	ADA
Location of clinical site: Canada										
IGA, n	24	50	48	50	48	30	67	33	67	33
IGA 0, n (%)	-	-	-	23 (46.0)	12 (25.0)	-	-	-	33 (49.3)	11 (33.3)
IGA 0/1, n (%)	0	43 (86.0)	28 (58.3)	43 (86.0)	26 (54.2)	2 (6.7)	46 (68.7)	24 (72.7)	48 (71.6)	22 (66.7)
PASI, n	24	50	48	50	48	30	67	33	67	33
PASI 90, n (%)	0	38 (76.0)	22 (45.8)	41 (82.0)	22 (45.8)	1 (3.3)	39 (58.2)	15 (45.5)	45 (67.2)	20 (60.6)
Location of clinical site: USA										
IGA, n	38	65	67	65	67	49	93	48	93	48
IGA 0, n (%)	-	-	-	38 (58.5)	15 (22.4)	-	-	-	43 (46.2)	12 (25.0)
IGA 0/1, n (%)	2 (5.3)	54 (83.1)	42 (62.7)	54 (83.1)	36 (53.7)	3 (6.1)	73 (78.5)	26 (54.2)	71 (76.3)	24 (50.0)
PASI, n	38	65	67	65	67	49	93	48	93	48
PASI 90, n (%)	1 (2.6)	46 (70.8)	25 (37.3)	51 (78.5)	29 (43.3)	2 (4.1)	63 (67.7)	19 (39.6)	68 (73.1)	21 (43.8)
Location of clinical site: Czech Republic										
IGA, n	-	-	-	-	-	9	14	8	14	8
IGA 0, n (%)	-	-	-	-	-	-	-	-	6 (42.9)	4 (50.0)
IGA 0/1, n (%)	-	-	-	-	-	0	14 (100.0)	6 (75.0)	13 (92.9)	6 (75.0)
PASI, n	-	-	-	-	-	9	14	8	14	8
PASI 90, n (%)	-	-	-	-	-	0	13 (92.9)	5 (62.5)	11 (78.6)	5 (62.5)

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	VOYAGE 1					VOYAGE 2				
	Week 16			Week 24		Week 16			Week 24	
	PBO	GUS	ADA	GUS	ADA	PBO	GUS	ADA	GUS	ADA
Location of clinical site: Hungary										
IGA, n	7	9	14	9	14	-	-	-	-	-
IGA 0, n (%)	-	-	-	6 (66.7)	5 (35.7)	-	-	-	-	-
IGA 0/1, n (%)	0	8 (88.9)	69 (65.1)	8 (88.9)	8 (57.1)	-	-	-	-	-
PASI, n	7	9	14	9	14	-	-	-	-	-
PASI 90, n (%)	0	8 (88.9)	7 (50.0)	8 (88.9)	8 (57.1)	-	-	-	-	-
Location of clinical site: Poland										
IGA, n	22	42	43	42	43	68	133	64	133	64
IGA 0, n (%)	-	-	-	29 (69.0)	21 (48.8)	-	-	-	78 (58.6)	22 (34.4)
IGA 0/1, n (%)	5 (22.7)	36 (85.7)	31 (72.1)	39 (92.9)	34 (79.1)	8 (11.8)	117 (88.0)	51 (79.7)	120 (90.2)	51 (79.7)
PASI, n	22	42	43	42	43	68	133	64	133	64
PASI 90, n (%)	3 (13.6)	36 (85.7)	25 (58.1)	38 (90.5)	29 (67.4)	1 (1.5)	95 (71.4)	35 (54.7)	108 (81.2)	42 (65.6)
Location of clinical site: Russia										
IGA, n	21	48	49	48	49	24	51	25	51	25
IGA 0, n (%)	-	-	-	22 (45.8)	18 (36.7)	-	-	-	30 (58.8)	13 (52.0)
IGA 0/1, n (%)	1 (4.8)	37 (77.1)	31 (63.3)	40 (83.3)	30 (61.2)	2 (8.3)	44 (86.3)	21 (84.0)	41 (80.4)	19 (76.0)
PASI, n	21	48	49	48	49	24	51	25	51	25
PASI 90, n (%)	0	37 (77.1)	28 (57.1)	39 (81.3)	29 (59.2)	1 (4.2)	41 (80.4)	17 (68.0)	41 (80.4)	18 (72.0)

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	VOYAGE 1					VOYAGE 2				
	Week 16			Week 24		Week 16			Week 24	
	PBO	GUS	ADA	GUS	ADA	PBO	GUS	ADA	GUS	ADA
Location of clinical site: Germany										
IGA, n	23	41	43	41	43	22	40	22	40	22
IGA 0, n (%)	-	-	-	18 (43.9)	9 (20.9)	-	-	-	17 (42.5)	4 (18.2)
IGA 0/1, n (%)	1 (4.3)	34 (82.9)	29 (67.4)	33 (80.5)	25 (58.1)	1 (4.5)	35 (87.5)	9 (40.9)	36 (90.0)	10 (45.5)
PASI, n	23	41	43	41	43	22	40	22	40	22
PASI 90, n (%)	0	21 (51.2)	17 (39.5)	29 (70.7)	22 (51.2)	0	26 (65.0)	6 (27.3)	31 (77.5)	6 (27.3)
Location of clinical site: Spain										
IGA, n	4	8	13	8	13	10	22	11	22	11
IGA 0, n (%)	-	-	-	6 (75.0)	10 (76.9)	-	-	-	14 (63.6)	3 (27.3)
IGA 0/1, n (%)	0	8 (100.0)	12 (92.3)	8 (100.0)	11 (84.6)	1 (10.0)	20 (90.9)	10 (90.9)	21 (95.5)	10 (90.9)
PASI, n	4	8	13	8	13	10	22	11	22	11
PASI 90, n (%)	0	8 (100.0)	11 (84.6)	8 (100.0)	10 (76.9)	0	14 (63.6)	6 (54.5)	18 (81.8)	7 (63.6)
Location of clinical site: Australia										
IGA, n	13	23	21	23	21	13	25	13	25	13
IGA 0, n (%)	-	-	-	11 (47.8	3 (14.3)	-	-	-	10 (40.0)	3 (23.1)
IGA 0/1, n (%)	1 (7.7)	29 (82.6)	16 (76.2)	17 (73.9)	12 (57.1)	0	23 (92.0)	8 (61.5)	19 (76.0)	7 (53.8)
PASI, n	13	23	21	23	21	13	25	13	25	13
PASI 90, n (%)	1 (7.7)	16 (69.6)	11 (52.4)	16 (69.6)	9 (42.9)	0	19 (76.0)	4 (30.8)	16 (64.0)	5 (38.5)

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	VOYAGE 1					VOYAGE 2				
	Week 16			Week 24		Week 16			Week 24	
	PBO	GUS	ADA	GUS	ADA	PBO	GUS	ADA	GUS	ADA
Location of clinical site: South Korea										
IGA, n	7	12	9	12	9	23	51	24	51	24
IGA 0, n (%)	-	-	-	7 (58.3)	1 (11.1)	-	-	-	26 (51.0)	6 (25.0)
IGA 0/1, n (%)	2 (28.6)	12 (100.0)	8 (88.9)	12 (100.0)	9 (100.0)	4 (17.4)	45 (88.2)	13 (54.2)	45 (88.2)	12 (50.0)
PASI, n	7	12	9	12	9	23	51	24	51	24
PASI 90, n (%)	0	8 (66.7)	6 (66.7)	11 (91.7)	7 (77.8)	1 (4.3)	37 (72.5)	9 (37.5)	35 (68.6)	12 (50.0)
Location of clinical site: Taiwan										
IGA, n	15	31	27	31	27	-	-	-	-	-
IGA 0, n (%)	-	-	-	13 (41.9)	4 (14.8)	-	-	-	-	-
IGA 0/1, n (%)	0	29 (93.5)	16 (59.3)	23 (74.2)	15 (55.6)	-	-	-	-	-
PASI, n	15	31	27	31	27	-	-	-	-	-
PASI 90, n (%)	0	23 (74.2)	14 (51.9)	23 (74.2)	12 (44.4)	-	-	-	-	-

Key: ADA, adalimumab; GUS, guselkumab; IGA, Investigator's Global Assessment; PASI, Psoriasis Area Severity Index; PBO, placebo.

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Table 5: Primary endpoint analyses of NAVIGATE based on the location of clinical site

	NAVIGATE	
	Week 28-40	
	GUS	UST
Location of clinical site: Canada		
N	6	11
Number of visits with an IGA score of 0/1 and ≥2-grade improvement week 28-40, mean (SD)	1.2 (1.83)	0.5 (1.29)
Location of clinical site: USA		
N	42	31
Number of visits with an IGA score of 0/1 and ≥2-grade improvement week 28-40, mean (SD)	1.3(1.63)	0.4 (1.06)
Location of clinical site: Germany		
N	24	22
Number of visits with an IGA score of 0/1 and ≥2-grade improvement week 28-40, mean (SD)	1.5 (1.35)	1.1 (1.55)
Location of clinical site: Poland		
N	36	37
Number of visits with an IGA score of 0/1 and ≥2-grade improvement week 28-40, mean (SD)	1.9 (1.59)	0.8 (1.28)
Location of clinical site: Russia		
N	5	6
Number of visits with an IGA score of 0/1 and ≥2-grade improvement week 28-40, mean (SD)	1.8 (1.79)	2.0 (1.90)
Location of clinical site: Spain		
N	-	2
Number of visits with an IGA score of 0/1 and ≥2-grade improvement week 28-40, mean (SD)	-	0.5 (0.71)
Location of clinical site: Australia		
N	3	4
Number of visits with an IGA score of 0/1 and ≥2-grade improvement week 28-40, mean (SD)	2.0 (1.73)	1.0 (1.15)
Location of clinical site: South Korea		
N	5	4

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	NAVIGATE	
	Week 28-40	
	GUS	UST
Number of visits with an IGA score of 0/1 and ≥2-grade improvement week 28-40, mean (SD)	1.6 (1.67)	0.5 (1.00)
Location of clinical site: Taiwan		
N	14	16
Number of visits with an IGA score of 0/1 and ≥2-grade improvement week 28-40, mean (SD)	1.1 (1.56)	0
Key: GUS, guselkumab; IGA, Investigator's Global Assessment; UST, ustekinumab.		

A6. **PRIORITY QUESTION**: To support consistency in the network meta-analyses, the company conducted pairwise conventional meta-analyses of PASI response for guselkumab compared with placebo and adalimumab, using the guselkumab trials (NMAs) (company submission section B.3.8 and appendix D figures 58–61). Please provide corresponding analyses using available evidence for other drugs included in the NMA networks, but especially for the chosen comparators (adalimumab and ustekinumab).

Pairwise conventional meta-analyses of PASI response (PASI 90 and PASI 75) and adverse event (AE) rates have been conducted for all comparisons relevant to the decision problem, using the restricted network of evidence. The results of the pairwise comparison are generally consistent with the results of the restricted NMA.

Outcomes of these analyses are summarised in Table 6; full results, including forest plots, are available in an attachment to this response document.

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Table 6: Summary of findings from pairwise conventional frequentist meta-analyses of PASI 75, PASI 90 and AE rates for all comparisons in the restricted network

Pairwise Comparisons	PASI 90		PASI 75		AE	
	Number of Studies (Sample Size)	Relative Risk (95% CI), I-squared(I^2)	Number of Studies (Sample Size)	Relative Risk (95% CI), I-squared(I^2)	Number of Studies (Sample Size)	Relative Risk (95% CI), I-squared(I^2)
Adalimumab 40 mg vs. Placebo	6 (2891)	14.97 (8.01 to 27.98), **I^2=60.4%**	6 (2891)	8.43 (6.03 to 11.78), **I^2=53.2%**	6 (2889)	1.06 (1 to 1.13), I^2=0.3%
Erelzi 50 mg vs. Etanercept 50 mg BIW	0(0)	NA	1 (531)	0.98 (0.88 to 1.1), I^2=NA	0 (0)	NA
Etanercept 25 mg BIW vs. Placebo	2 (717)	10.27 (3.72 to 28.38), I^2=0%	2 (717)	9.31 (5.35 to 16.18), I^2=0%	0(0)	NA
Etanercept 50 mg BIW vs. Etanercept 25 mg BIW	2 (716)	1.88 (1.32 to 2.66), I^2=0%	2 (716)	1.43 (1.2 to 1.72), I^2=0%	0(0)	NA
Etanercept 50 mg BIW vs. Etanercept 50 mg QW	1 (270)	2.68 (1.55 to 4.62), I^2=NA	1 (270)	1.68 (1.3 to 2.16), I^2=NA	1 (273)	1.08 (0.91 to 1.27), I^2=NA
Etanercept 50 mg BIW vs. Ixekizumab 80 mg Q2W	2 (1476)	0.32 (0.22 to 0.45), **I^2=82.4%**	2 (1476)	0.53 (0.41 to 0.7), **I^2=91.2%**	2(1473)	0.94 (0.86 to 1.03), I^2=0%
Etanercept 50 mg BIW vs. Placebo	10 (4413)	12.87 (8.43 to 19.65), I^2=11.1%	10 (4413)	9.28 (7.53 to 11.43), I^2=0%	8 (3698)	1.12 (1.05 to 1.2), I^2=0%
Etanercept 50 mg BIW vs. Secukinumab 150 mg	1 (650)	0.5 (0.39 to 0.63), I^2=NA	1 (650)	0.66(0.57 to 0.76), I^2=NA	1 (650)	0.99 (0.86 to 1.12), I^2=NA
Etanercept 50 mg BIW vs. Secukinumab 300 mg	1 (646)	0.38 (0.3 to 0.48), I^2=NA	1 (646)	0.57 (0.5 to 0.65), I^2=NA	1 (649)	1.04 (0.91 to 1.19), I^2=NA

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Pairwise Comparisons	PASI 90		PASI 75		AE	
	Number of Studies (Sample Size)	Relative Risk (95% CI), I-squared(I^2)	Number of Studies (Sample Size)	Relative Risk (95% CI), I-squared(I^2)	Number of Studies (Sample Size)	Relative Risk (95% CI), I-squared(I^2)
Etanercept 50 mg QW vs. Placebo	2 (309)	5.86 (2.11 to 16.29), I^2=0%	2 (309)	6.49 (1.49 to 28.2), **I^2=57.2%**	1 (167)	0.99 (0.74 to 1.31), I^2=NA
Guselkumab 100 mg vs. Adalimumab 40 mg	2 (1407)	1.48 (1.35 to 1.63), I^2=0%	2 (1407)	1.25 (1.18 to 1.33), I^2=0%	2 (1404)	1 (0.9 to 1.11), I^2=0%
Guselkumab 100 mg vs. Placebo	2 (1247)	27.3 (15.21 to 49), I^2=0%	2 (1247)	12.26 (8.48 to 17.74), I^2=10.1%	2 (1245)	1.05 (0.93 to 1.19), I^2=0%
Infliximab 5 mg/kg vs. Etanercept 50 mg BIW	1 (48)	10.14 (0.59 to 173.56), I^2=NA	1 (48)	3.5 (1.56 to 7.83), I^2=NA	1 (48)	0.96 (0.89 to 1.04), I^2=NA
Infliximab 5 mg/kg vs. Placebo	4 (1083)	51.61 (16.71 to 159.35), I^2=0%	4 1084)	35.52 (17.48 to 72.17), I^2=0%	4 (1082)	1.22 (1.09 to 1.35), I^2=9.3%
Ixekizumab 80 mg Q2W vs. Placebo	3 (1961)	65.01 (13.97 to 302.56), **I^2=75.2%**	3 (1961)	19.87 (10.99 to 35.91), **I^2=65.1%**	3 (1958)	1.26 (1.11 to 1.42),I^2=39.9%
Secukinumab 150 mg vs. Placebo	4 (1380)	30.84 (16.02 to 59.39), I^2=0%	4 (1381)	15.36 (10.76 to 21.94), I^2=0%	4 (1386)	1.21 (1.1 to 1.34), I^2=0%
Secukinumab 300 mg vs. Placebo	4 (1377)	42.26 (22.01 to 81.15), I^2=0%	4 (1378)	17.65 (12.38 to 25.17), I^2=0%	4 (1384)	1.15 (1.04 to 1.27), I^2=0%
Secukinumab 300 mg vs. Secukinumab 150 mg	5 (2343)	1.34 (1.24 to 1.45), I^2=0%	5 (2344)	1.1 (1.06 to 1.14), I^2=3%	5 (2347)	0.97 (0.9 to 1.04), I^2=0%
Ustekinumab 45 mg vs. Etanercept 50 mg BIW	1 (556)	1.58 (1.21 to 2.05), I^2=NA	1 (556)	1.19 (1.04 to 1.36), I^2=NA	1 (556)	0.94 (0.84 to 1.06), I^2=NA

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Pairwise Comparisons	PASI 90		PASI 75		AE	
	Number of Studies (Sample Size)	Relative Risk (95% CI), I-squared(I^2)	Number of Studies (Sample Size)	Relative Risk (95% CI), I-squared(I^2)	Number of Studies (Sample Size)	Relative Risk (95% CI), I-squared(I^2)
Ustekinumab 45 mg vs. Placebo	5 (1867)	25.39 (15.31 to 42.09), I^2=0%	5 (1867)	13.12 (7.82 to 22.02), I^2=62.5%	5 (1867)	1.08 (0.99 to 1.18), I^2=0%
Ustekinumab 45/90 mg vs. Ixekizumab 80 mg Q2W	1 (302)	0.58 (0.47 to 0.71), I^2=NA	1 (302)	0.78 (0.69 to 0.88), I^2=NA	1 (301)	1.08 (0.94 to 1.25), I^2=NA
Ustekinumab 45/90 mg vs. Placebo	2 (1237)	19.28 (11.61 to 32.01), I^2=0%	2 (1237)	9.75 (7.3 to 13.03), I^2=0%	2 (1235)	1.11 (1 to 1.23), I^2=0%
Ustekinumab 45/90 mg vs. Secukinumab 300 mg	1 (669)	0.73 (0.65 to 0.83), I^2=NA	1 (669)	0.87 (0.81 to 0.93), I^2=NA	1 (671)	0.91 (0.81 to 1.03), I^2=NA
Ustekinumab 90 mg vs. Etanercept 50 mg BIW	1 (694)	1.94 (1.55 to 2.43), I^2=NA	1 (694)	1.3 (1.16 to 1.45), I^2=NA	1 (694)	0.99 (0.9 to 1.09), I^2=NA
Ustekinumab 90 mg vs. Placebo	3 (1425)	28.33 (10.09 to 79.49), **I^2=52.2%**	3 (1425)	19.71 (13.38 to 29.03), I^2=0%	3 (1425)	0.99 (0.89 to 1.1), I^2=0%
Ustekinumab 90 mg vs. Ustekinumab 45 mg	4 (2013)	1.13 (0.95 to 1.33), **I^2=55.2%**	4 (2013)	1.09 (1.02 to 1.16), I^2=7.7%	4 (2012)	0.95 (0.87 to 1.04),I^2=22.5%

Key: AE, adverse event; CI, confidence interval; NA, not applicable.

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A7. **PRIORITY QUESTION**: The following priority questions relate to the NMA:

a) Please reproduce the NMA using change of DLQI score as the outcome

Both the NMA utilising the full evidence network and the NMA utilising the restricted evidence network have been reproduced using the change of DLQI score as requested. Evidence networks and outcomes of these analyses are provided in Figure 3 to Figure 6.

Given that the change of DLQI score was a secondary outcome in randomised controlled trials (RCTs) identified, several studies did not report sufficient data for inclusion in this reproduced NMA. The results provided are based on RCTs which reported data on mean differences from baseline and standard error (SE) or standard deviation (SD) or 95% confidence interval (CI) for each treatment arm, or mean differences between treatment arms. No imputation was undertaken due to the reduced timeframe for response.

Similar to previous findings reported from NMAs for other efficacy outcomes, guselkumab demonstrates comparable or greater efficacy compared with alternative biologics at the end of induction in terms of using the change of DLQI score as the outcome.

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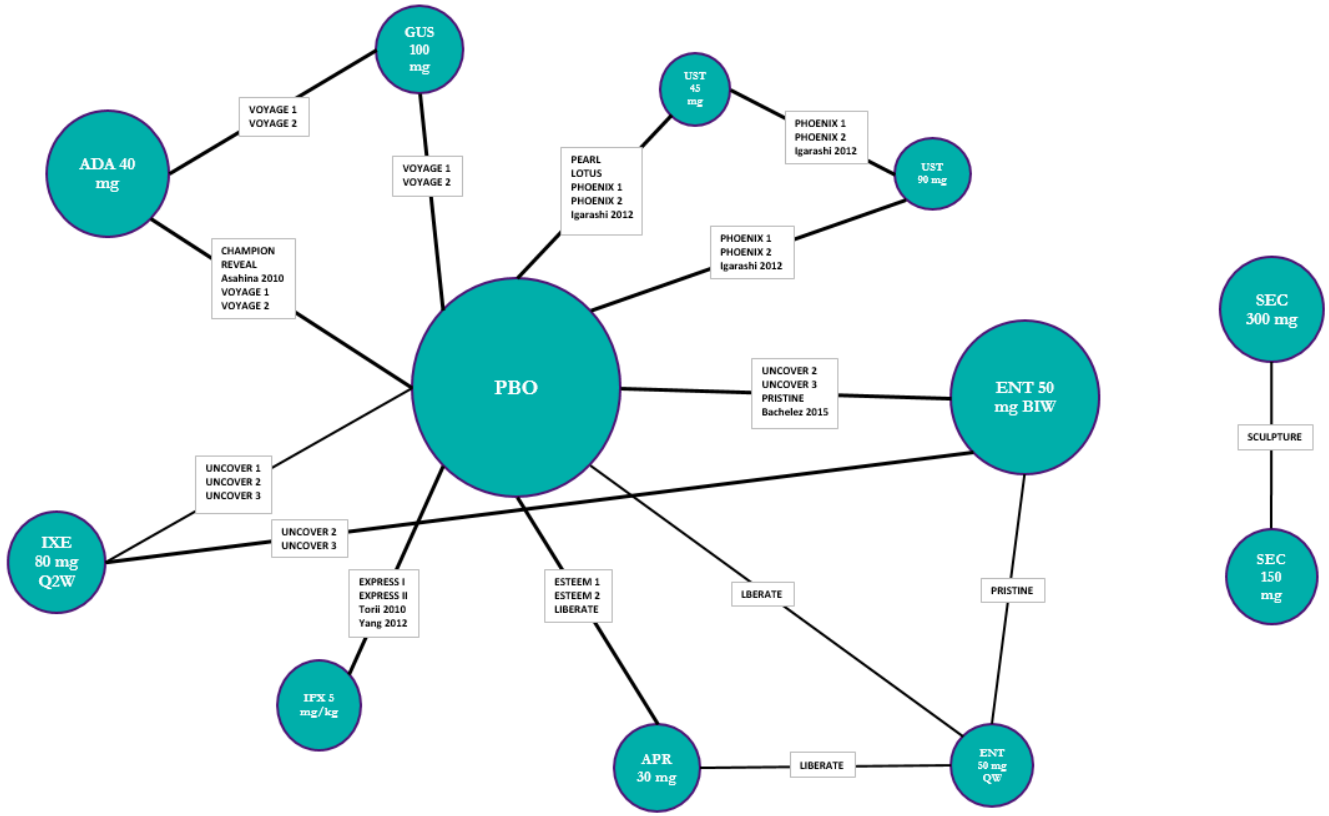
Figure 3: Full evidence network for mean change in DLQI at the end of induction



Key: ADA, adalimumab; BIW, biweekly; BRO, brodalumab; ENT, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; PBO, placebo; QW, once weekly; Q2W, every two weeks; SEC, secukinumab; UST, ustekinumab.

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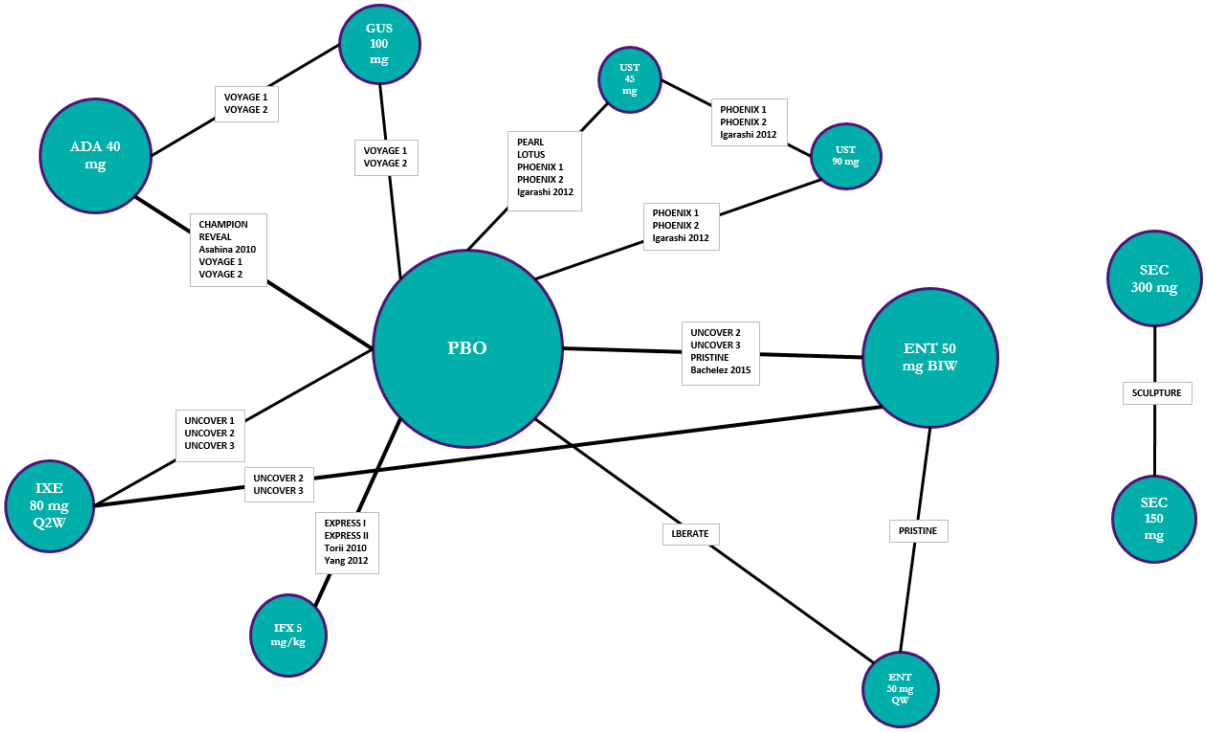
Figure 4: Restricted evidence network for mean change in DLQI at the end of induction



Key: ADA, adalimumab; BIW, biweekly; BRO, brodalumab; ENT, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; PBO, placebo; QW, once weekly; Q2W, every two weeks; SEC, secukinumab; UST, ustekinumab.

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Figure 5: League table summary of difference in DLQI change from baseline at the end of induction analyses; full evidence network

Guselkumab 100 mg									
-0.12 (-2.03 to 1.80)	Infliximab 5 mg/kg								
-0.28 (-2.01 to 1.51)	-0.15 (-1.80 to 1.57)	Ixekizumab 80 mg Q2W							
-0.68 (-2.53 to 1.18)	-0.57 (-2.34 to 1.21)	-0.41 (-2.07 to 1.18)	Ustekinumab 90 mg						
-1.13 (-2.84 to 0.63)	-1.02 (-2.63 to 0.70)	-0.86 (-2.32 to 0.63)	-0.45 (-1.76 to 0.96)	Ustekinumab 45 mg					
-2.34 (-3.85 to -0.80)	-2.22 (-3.84 to -0.54)	-2.07 (-3.53 to -0.62)	-1.65 (-3.23 to -0.06)	-1.21 (-2.66 to 0.22)	Adalimumab 40 mg				
-2.95 (-4.66 to -1.13)	-2.83 (-4.46 to -1.09)	-2.67 (-3.92 to -1.38)	-2.26 (-3.85 to -0.60)	-1.82 (-3.27 to -0.33)	-0.61 (-2.03 to 0.89)	Etanercept 50 mg BIW			
-5.01 (-6.87 to -3.08)	-4.89 (-6.66 to -3.03)	-4.74 (-6.38 to -3.09)	-4.32 (-6.04 to -2.54)	-3.87 (-5.52 to -2.26)	-2.67 (-4.28 to -1.04)	-2.07 (-3.69 to -0.47)	Apremilast 30 mg		
-5.19 (-7.39 to -2.89)	-5.07 (-7.22 to -2.86)	-4.91 (-6.86 to -2.94)	-4.50 (-6.60 to -2.33)	-4.05 (-6.08 to -2.04)	-2.85 (-4.84 to -0.81)	-2.24 (-3.96 to -0.55)	-0.17 (-2.23 to 1.88)	Etanercept 50 mg QW	
-9.33 (-10.71 to -7.89)	-9.21 (-10.48 to -7.88)	-9.06 (-10.12 to -8.00)	-8.65 (-9.84 to -7.39)	-8.20 (-9.24 to -7.19)	-6.99 (-7.99 to -5.96)	-6.38 (-7.46 to -5.35)	-4.32 (-5.59 to -3.07)	-4.15 (-5.90 to -2.42)	Placebo

Key: BIW, biweekly; QW, once weekly; Q2W, every 2 weeks.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of mean differences and 95% credible intervals. A mean difference <0 favours treatment in a given column.

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Figure 6: League table summary of difference in DLQI change from baseline at the end of induction analyses; restricted evidence network

Guselkumab 100 mg								
-0.13 (-2.13 to 1.87)	Infliximab 5 mg/kg							
-0.25 (-2.09 to 1.65)	-0.13 (-1.85 to 1.69)	Ixekizumab 80 mg Q2W						
-0.69 (-2.65 to 1.29)	-0.57 (-2.43 to 1.36)	-0.44 (-2.18 to 1.28)	Ustekinumab 90 mg					
-1.11 (-2.90 to 0.80)	-0.98 (-2.66 to 0.81)	-0.85 (-2.40 to 0.75)	-0.41 (-1.81 to 1.05)	Ustekinumab 45 mg				
-2.33 (-3.91 to -0.70)	-2.21 (-3.90 to -0.43)	-2.07 (-3.65 to -0.52)	-1.64 (-3.33 to 0.07)	-1.23 (-2.78 to 0.27)	Adalimumab 40 mg			
-2.92 (-4.72 to -0.99)	-2.80 (-4.50 to -0.97)	-2.67 (-4.00 to -1.29)	-2.23 (-3.91 to -0.45)	-1.81 (-3.39 to -0.21)	-0.59 (-2.12 to 1.01)	Etanercept 50 mg BIW		
-5.15 (-7.44 to -2.78)	-5.03 (-7.21 to -2.68)	-4.90 (-6.91 to -2.83)	-4.46 (-6.66 to -2.18)	-4.05 (-6.17 to -1.90)	-2.82 (-4.91 to -0.68)	-2.23 (-4.02 to -0.46)	Etanercept 50 mg QW	
-9.32 (-10.76 to -7.79)	-9.19 (-10.51 to -7.78)	-9.07 (-10.20 to -7.92)	-8.63 (-9.91 to -7.29)	-8.22 (-9.32 to -7.14)	-6.99 (-8.05 to -5.90)	-6.40 (-7.56 to -5.28)	-4.17 (-6.01 to -2.37)	Placebo

Key: BIW, biweekly; QW, once weekly; Q2W, every 2 weeks.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of man differences and 95% credible intervals. A mean difference <0 favours treatment in a given column.

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b) Please provide results of tests comparing inconsistency and consistency models, namely the DIC for the inconsistency models.

Results of tests comparing inconsistency and consistency models for unadjusted relative effects analyses are provided in Table 7.

Results of tests comparing inconsistency and consistency models for risk difference analyses are provided in Table 8.

Table 7: Summary of inconsistency and consistency model fit statistics from unadjusted relative effects NMAs

	PASI 90	IGA & PGA	PASI 100	PASI 75	PASI 50	DLQI	AE	SAE	WDAE
Unadjusted – Restricted Network – Consistency Model	DIC: 560.76 Resdev: 87.84 vs. 93 data points	DIC: 602.45 Resdev: 95.65 vs. 93 data points	DIC: 349.97 Resdev: 57.33 vs. 63 data points	DIC: 600.62 Resdev: 88.37 vs. 95 data points	DIC: 336.67 Resdev: 50.45 vs. 54 data points	DIC: 381.61 Resdev: 56.59 vs. 56 data points	DIC: 589.61 Resdev: 80.66 vs. 85 data points	DIC: 389.17 Resdev: 78.05 vs. 87 data points	DIC: 394.48 Resdev: 74.92 vs. 92 data points
Unadjusted – Restricted Network – Inconsistency Model	DIC: 568.93 Resdev: 98.82 vs. 93 data points	DIC: 607.94 Resdev: 95.23 vs. 93 data points	DIC: 355.68 Resdev: 60.61 vs. 63 data points	DIC: 609.17 Resdev: 90.17 vs. 95 data points	DIC: 336.93 Resdev: 48.82 vs. 54 data points	DIC: 386.54 Resdev: 58.03 vs. 56 data points	DIC: 593.16 Resdev: 78.67 vs. 85 data points	DIC: 395.74 Resdev: 78.93 vs. 87 data points	DIC: 399.46 Resdev: 74.80 vs. 92 data points
Unadjusted – Full Network – Consistency Model	DIC: 693.17 Resdev: 110.09 vs. 112 data points	DIC: 736.24 Resdev: 114.35 vs. 112 data points	DIC: 446.37 Resdev: 70.65 vs. 77 data points	DIC: 735.92 Resdev: 107.04 vs. 114 data points	DIC: 387.75 Resdev: 58.87 vs. 61 data points	DIC: 505.75 Resdev: 74.73 vs. 73 data points	DIC: 735.06 Resdev: 99.37 vs. 104 data points	DIC: 485.37 Resdev: 96.53 vs. 106 data points	DIC: 485.88 Resdev: 91.63 vs. 111 data points

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Unadjusted – Full Network – Inconsistency Model	DIC: 705.23 Resdev: 115.38 vs. 112 data points	DIC: 743.78 Resdev: 115.40 vs. 112 data points	DIC: 458.92 Resdev: 78.27 vs. 77 data points	DIC: 737.97 Resdev: 108.18 vs. 114 data points	DIC: 386.50 Resdev: 56.53 vs. 61 data points	DIC: 511.01 Resdev: 77.06 vs. 73 data points	DIC: 737.09 Resdev: 96.11 vs. 104 data points	DIC: 491.54 Resdev: 97.33 vs. 106 data points	DIC: 491.19 Resdev: 91.91 vs. 111 data points
Key: AE, adverse event; DIC, deviance information criteria; DLQI, Dermatology Life Quality Index; IGA, Investigator Global Assessment; NA, not applicable; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; Resdev, residual deviance; SAE, serious adverse event; WDAE, withdrawal due to an adverse event.									

Table 8: Summary of inconsistency and consistency model fit statistics from risk difference NMAs

	PASI 90	**IGA & PGA**	**PASI 100**	**PASI 75**	**PASI 50**	**DLQI**	**AE**	**SAE**	**WDAE**
Unadjusted – Restricted Network – Consistency Model	DIC: 567.31 Resdev: 92.43 vs. 93 data points	DIC: 607.22 Resdev: 93.54 vs. 93 data points	DIC: 357.44 Resdev: 66.55 vs. 63 data points	DIC: 617.06 Resdev: 96.95 vs. 95 data points	DIC: 346.80 Resdev: 56.30 vs. 54 data points	DIC: 397.55 Resdev: 56.33 vs. 56 data points	DIC: 596.73 Resdev: 83.36 vs. 85 data points	DIC: 397.21 Resdev: 71.11 vs. 87 data points	DIC: 407.27 Resdev: 79.40 vs. 92 data points
Unadjusted – Restricted Network – Inconsistency Model	DIC: 573.11 Resdev: 93.66 vs. 93 data points	DIC: 611.21 Resdev: 93.18 vs. 93 data points	DIC: 358.27 Resdev: 58.35 vs. 63 data points	DIC: 618.24 Resdev: 88.73 vs. 95 data points	DIC: 348.13 Resdev: 48.05 vs. 54 data points	DIC: 403.95 Resdev: 60.28 vs. 56 data points	DIC: 599.51 Resdev: 80.50 vs. 85 data points	DIC: 406.28 Resdev: 83.80 vs. 87 data points	DIC: 420.87 Resdev: 80.38 vs. 92 data points
Unadjusted – Full Network – Consistency Model	DIC: 689.80 Resdev: 111.83 vs. 112	DIC: 746.37 Resdev: 118.38 vs. 112	DIC: 460.59 Resdev: 87.77 vs. 77 data points	DIC: 757.72 Resdev: 114.72 vs. 114	DIC: 388.12 Resdev: 64.72 vs. 61 data points	DIC: 512.18 Resdev: 78.92 vs. 73 data points	DIC: 744.26 Resdev: 104.26 vs. 104	DIC: 486.72 Resdev: 103.40 vs. 106	DIC: 495.26 Resdev: 110.30 vs. 111

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	data points	data points		data points			data points	data points	data points
Unadjusted – Full Network – Inconsistency Model	DIC: 694.50 Resdev: 112.39 vs. 112 data points	DIC: 749.13 Resdev: 118.59 vs. 112 data points	DIC: 462.95 Resdev: 91.19 vs. 77 data points	DIC: 757.92 Resdev: 113.17 vs. 114 data points	DIC: 389.47 Resdev: 63.52 vs. 61 data points	DIC: 515.66 Resdev: 79.15 vs. 73 data points	DIC: 747.63 Resdev: 106.72 vs. 104 data points	DIC: 488.76 Resdev: 104.58 vs. 106 data points	DIC: 499.65 Resdev: 113.17 vs. 111 data points
Key: AE, adverse event; DIC, deviance information criteria; DLQI, Dermatology Life Quality Index; IGA, Investigator Global Assessment; NA, not applicable; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; Resdev, residual deviance; SAE, serious adverse event; WDAE, withdrawal due to an adverse event.									

c) The ERG has concerns about the difference in evidence networks between the 'full' network and the 'restricted' network (described in the company submission as the decision comparator set or focussed network [page 74 document B]). It appears that the company prioritised the broader evidence networks, which contradicts the company view on the treatment pathway (figure 1 company submission), namely that guselkumab would be used after treatments that were included in the full network (for example, apremilast).

To clarify, the company submission describes the synthesised evidence network used in base case analyses as broader than the decision comparator set. This full network aligns with the full breadth of treatments considered in the SLR protocol and search strategy, and allows leverage of additional studies investigating the treatment of plaque psoriasis to better adjust for heterogeneity.

A sensitivity analyses that Restricted the synthesised evidence network to trials investigating biologic treatments relevant to NHS practice was also conducted for the outcome of PASI 90. This sensitivity analyses demonstrated that results do not differ between the full network and restricted network analyses and supported the use of the full network but with result presentation restricted to the decision comparator set of relevance.

To mitigate ERG concerns, we have since run analyses using the restricted network for other outcomes (that is, PASI 75, PASI 100, DLQI, AE, serious adverse event [SAE],

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withdrawal due to adverse event [WDAE]). As observed for PASI 90, results from these analyses corroborate results previously presented from the full evidence network.

i. It appears that the “full network” is presented in Appendix D, please confirm that this is correct.

We can confirm that the full evidence networks are provided in Appendix D.

ii. Please provide the study-inclusion criteria and network diagrams for the ‘restricted networks’ / ‘focussed networks’ / ‘sensitivity analysis’

Study-inclusion criteria for the restricted network were as per study-inclusion for the full evidence network (presented in Table 4 of Appendix D) but with treatments of interest restricted to those relevant to NHS practice, as summarised in Table 9.

Restricted network diagrams for the key outcomes analysed (PASI 90, PASI 75 and AE) are provided in Figure 7, Figure 8 and Figure 9.

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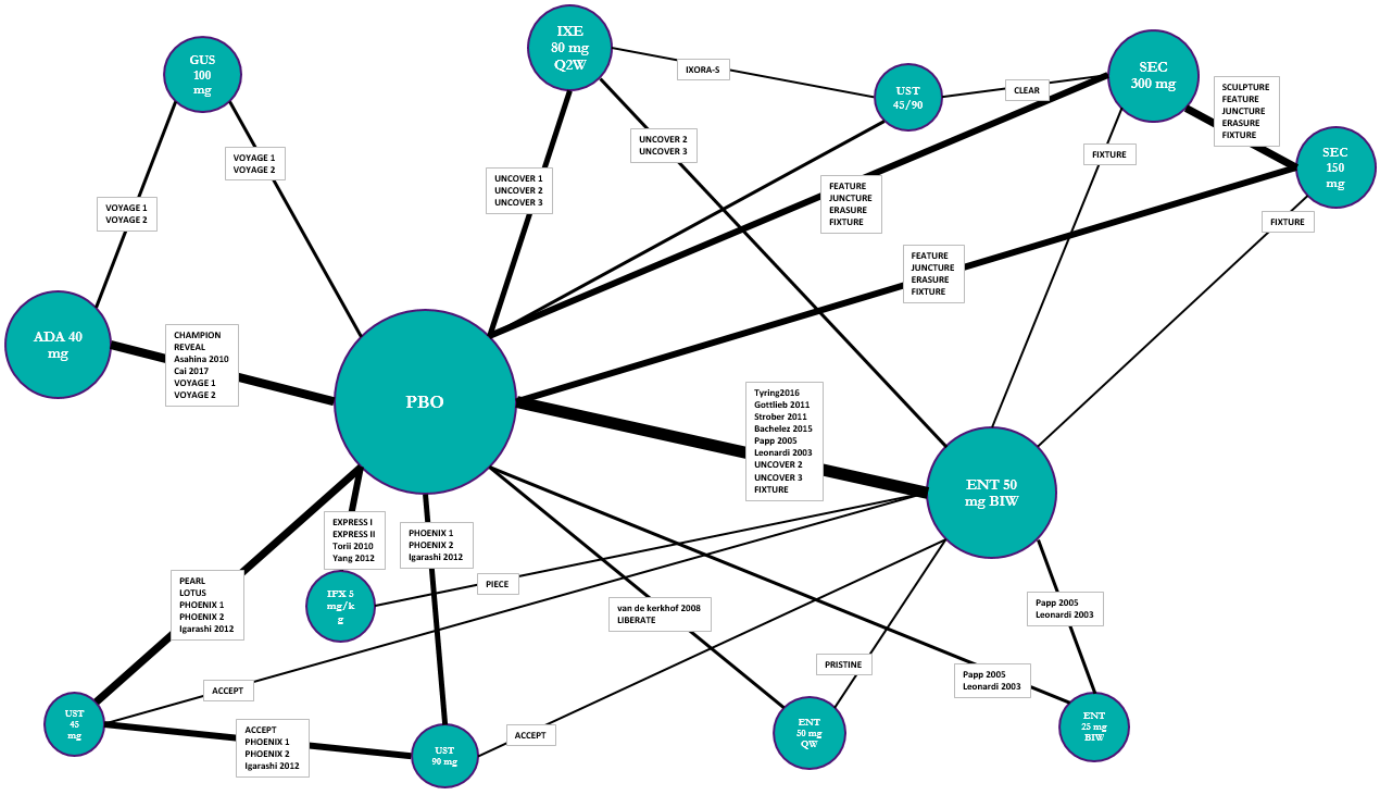
Figure 7: Restricted evidence network for PASI 90 response at the end of induction



Key: ADA, adalimumab; BIW, biweekly; BRO, brodalumab; ENT, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; PBO, placebo; QW, once weekly; Q2W, every two weeks; SEC, secukinumab; UST, ustekinumab.

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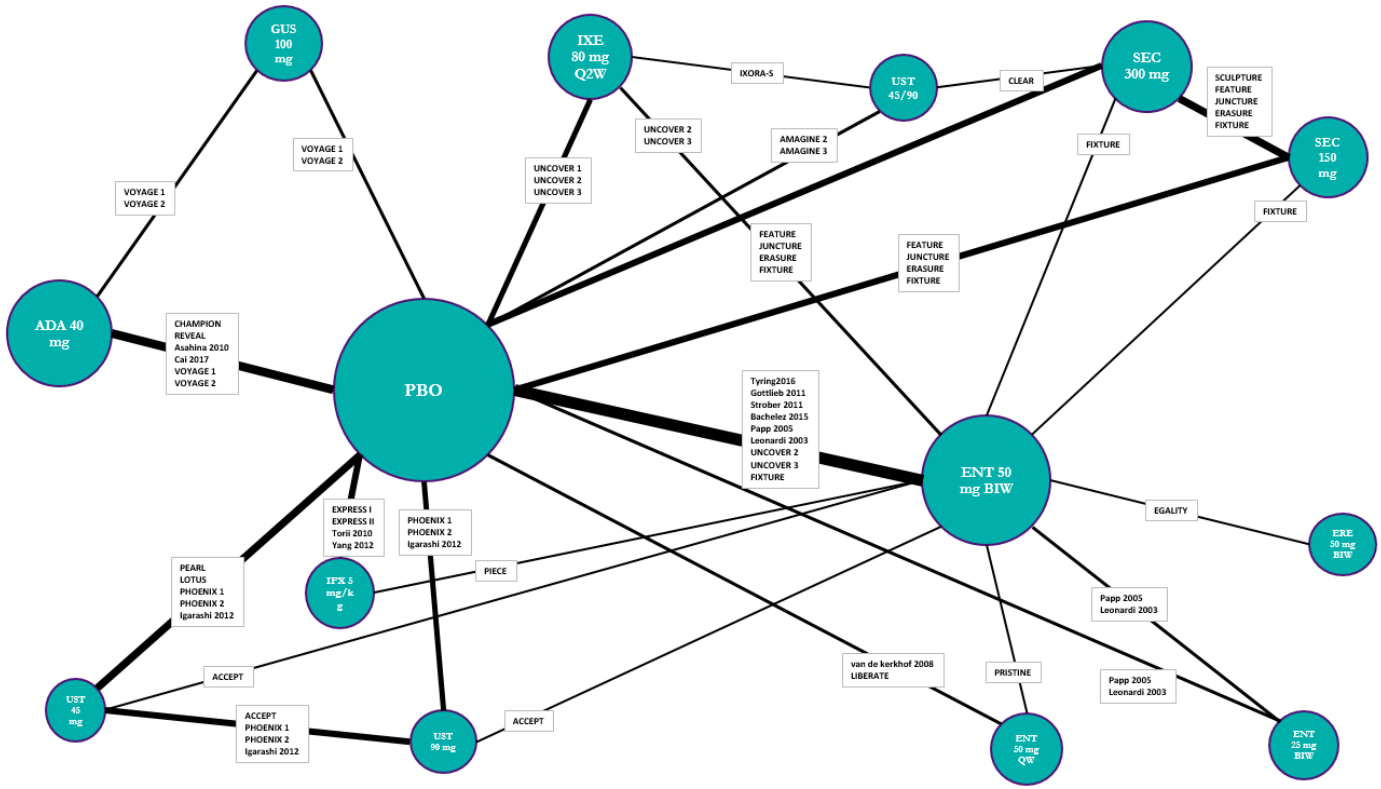
Figure 8: Restricted evidence network for PASI 75 response at the end of induction



Key: ADA, adalimumab; BIW, biweekly; BRO, brodalumab; ENT, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; PBO, placebo; QW, once weekly; Q2W, every two weeks; SEC, secukinumab; UST, ustekinumab.

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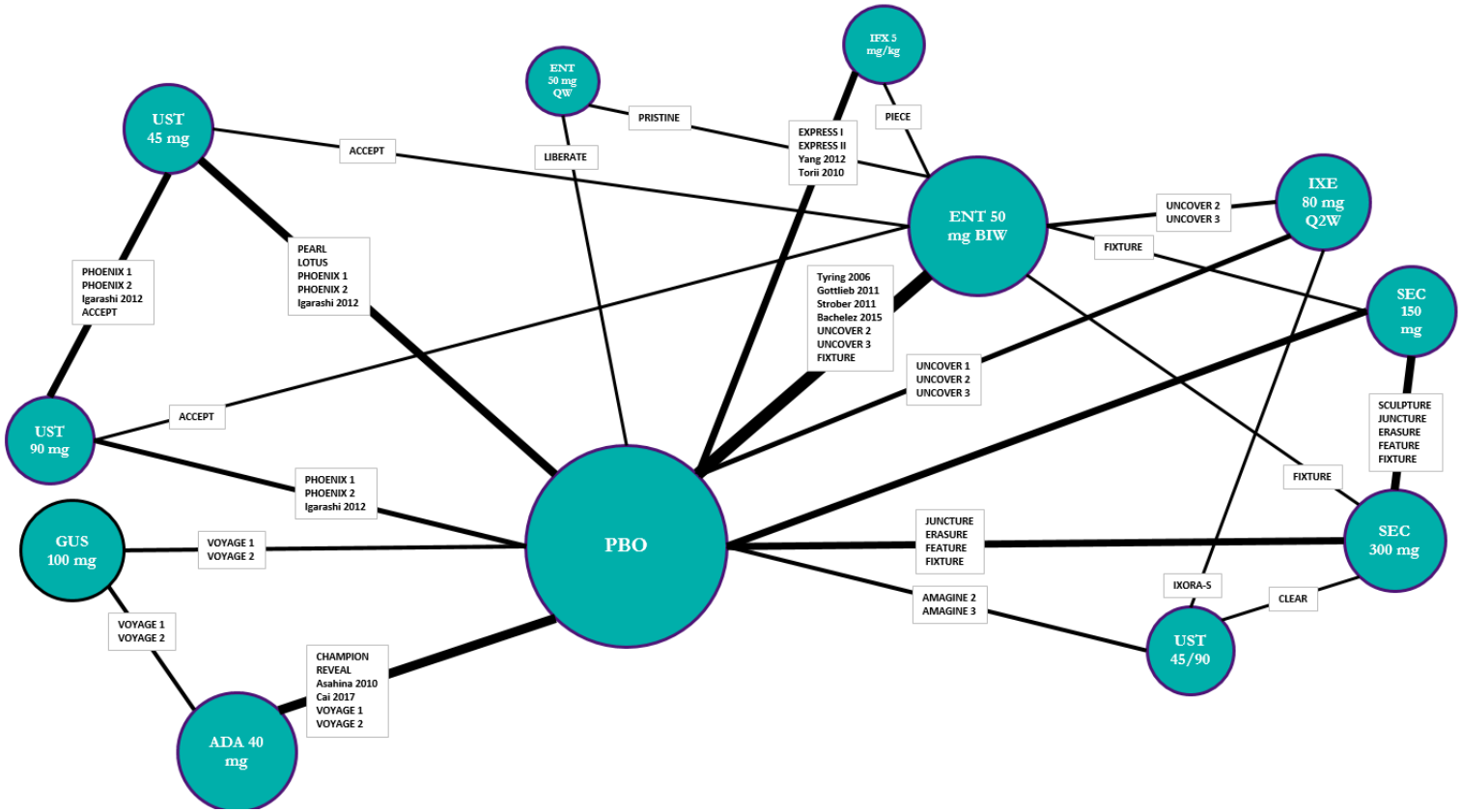
Figure 9: Restricted evidence network for AE rate at the end of induction



Key: ADA, adalimumab; BIW, biweekly; BRO, brodalumab; ENT, etanercept; GUS, guselkumab; IFX, infliximab; IXE, ixekizumab; PBO, placebo; QW, once weekly; Q2W, every two weeks; SEC, secukinumab; UST, ustekinumab.

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iii. Please also confirm that the decision comparator set NMA should be considered as the primary NMA for this submission.

The restricted network NMA reported in this reply is the decision comparator set NMA and therefore it should be considered the primary NMA for this submission. Nevertheless, the full network (global network) yields similar results for treatments considered in the decision problem and it provides a more detailed assessment of heterogeneity due to its larger size.

d) Please clearly define the different NMAs presented in terms of treatments included (for example, Decision comparator set [13-14 treatments], full network [19 treatments]).

An overview of the number of trials and treatments included in each NMA is provided in Table 9.

Table 9: Trials and treatments included in NMAs presented

	Restricted Network (Decision Comparator Network)	**Full Network (Global Network)**
Number of RCTs	PASI 90: 39 studies PASI 75: 40 studies AEs: 36 studies	PASI 90: 44 studies PASI 75: 45 studies AEs: 41 studies
Number of Treatments	PASI 90: 13 treatments PASI 75: 14 treatments AEs: 12 treatments	PASI 90: 19 treatments PASI 75: 20 treatments AEs: 18 treatments

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	Restricted Network (Decision Comparator Network)	Full Network (Global Network)
List of treatments considered including doses	Guselkumab 100 mg Ixekizumab 80 mg Q2W Secukinumab 300 mg Secukinumab 150 mg Ustekinumab 45/90 mg Ustekinumab 90 mg Ustekinumab 45 mg Infliximab 5 mg/kg Adalimumab 40 mg Etanercept 50 mg BIW Etanercept 50 mg QW Etanercept 25 mg BIW Erelzi 50 mg BIW Placebo	Guselkumab 100 mg Ixekizumab 80 mg Q2W Secukinumab 300 mg Secukinumab 150 mg Brodalumab 140 mg Brodalumab 210 mg Tildrakizumab 200 mg Tildrakizumab 100 mg Ustekinumab 45/90 mg Ustekinumab 90 mg Ustekinumab 45 mg Infliximab 5 mg/kg Adalimumab 40 mg ABP 501 40 mg Etanercept 50 mg BIW Etanercept 50 mg QW Etanercept 25 mg BIW Erelzi 50 mg BIW Apremilast 30 mg Placebo

Key: BIW, biweekly; NMA, network meta-analysis; PASI, Psoriasis Area Severity Index; Q2W, every two weeks; QW, once weekly.

e) ABP 501 (adalimumab biosimilar) appears in Figure 13 of Document B of the company submission, but not Figure 12. Please update NMA results as necessary.

Adalimumab biosimilar (ABP 501) is not available in the NHS and should not have been included in the restricted network analyses. Please find corrected baseline risk-adjusted NMA results for PASI 90 response and further results for PASI 75 provided in Figure 10 and Figure 11.

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Figure 10: League table summary of relative risks for the PASI 90 response at the end of induction analyses; baseline risk-adjusted; restricted evidence network

Ixekizumab 80 mg Q2W												
1.01 (0.89 – 1.15)	**Guselkumab 100 mg**											
1.20 (1.06 – 1.36)	1.19 (1.02 – 1.38)	**Secukinumab 300 mg**										
1.29 (1.10 – 1.53)	1.29 (1.06 – 1.56)	1.08 (0.91 – 1.30)	**Infliximab 5 mg/kg**									
1.49 (1.29 – 1.73)	1.48 (1.30 – 1.68)	1.24 (1.05 – 1.47)	1.15 (0.94 – 1.42)	**Adalimumab 40 mg**								
1.52 (1.30 – 1.79)	1.51 (1.26 – 1.81)	1.27 (1.07 – 1.52)	1.17 (0.95 – 1.44)	1.02 (0.84 – 1.24)	**Ustekinumab 90 mg**							
1.57 (1.36 – 1.83)	1.56 (1.32 – 1.84)	1.31 (1.11 – 1.55)	1.21 (0.99 – 1.48)	1.06 (0.88 – 1.27)	1.04 (0.89 – 1.21)	**Ustekinumab 45 mg**						
1.63 (1.39 – 1.94)	1.62 (1.35 – 1.97)	1.36 (1.15 – 1.63)	1.26 (1.01 – 1.58)	1.10 (0.90 – 1.35)	1.08 (0.86 – 1.34)	1.04 (0.85 – 1.28)	**Ustekinumab 45/90 mg**					
1.64 (1.39 – 1.96)	1.63 (1.35 – 1.98)	1.37 (1.20 – 1.59)	1.27 (1.03 – 1.57)	1.11 (0.90 – 1.36)	1.09 (0.88 – 1.34)	1.05 (0.85 – 1.28)	1.01 (0.81 – 1.25)	**Secukinumab 150 mg**				
3.05 (2.66 – 3.50)	3.03 (2.54 – 3.58)	2.54 (2.18 – 2.98)	2.35 (1.94 – 2.83)	2.05 (1.69 – 2.46)	2.01 (1.68 – 2.40)	1.94 (1.63 – 2.30)	1.87 (1.52 – 2.28)	1.85 (1.53 – 2.24)	**Etanercept 50 mg BIW**			
5.33 (3.67 – 7.99)	5.29 (3.62 – 7.98)	4.45 (3.05 – 6.72)	4.11 (2.76 – 6.33)	3.58 (2.44 – 5.42)	3.51 (2.37 – 5.37)	3.39 (2.30 – 5.15)	3.27 (2.19 – 4.99)	3.24 (2.17 – 4.98)	1.75 (1.20 – 2.62)	**Etanercept 50 mg QW**		
5.92 (4.01 – 8.95)	5.88 (3.93 – 9.01)	4.94 (3.32 – 7.51)	4.57 (3.04 – 7.00)	3.98 (2.63 – 6.13)	3.90 (2.59 – 5.98)	3.77 (2.51 – 5.76)	3.63 (2.37 – 5.63)	3.60 (2.38 – 5.55)	1.94 (1.32 – 2.92)	1.11 (0.64 – 1.92)	**Etanercept 25 mg BIW**	
41.44 (38.01 – 44.51)	41.21 (36.87 – 44.98)	34.61 (30.87 – 38.23)	31.97 (27.16 – 37.25)	27.87 (24.52 – 31.13)	27.31 (23.33 – 31.39)	26.35 (22.94 – 29.87)	25.41 (21.40 – 29.48)	25.18 (21.26 – 29.31)	13.58 (11.87 – 15.49)	7.77 (5.20 – 11.18)	6.99 (4.63 – 10.31)	**Placebo**

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR >1 favours treatment in a given column.

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Figure 11: League table summary of relative risks for the PASI 75 response at the end of induction analyses; baseline risk-adjusted; restricted evidence network

Ixekizumab 80 mg Q2W												
1.02 (0.97 – 1.07)	**Guselkumab 100 mg**											
1.08 (1.01 – 1.16)	1.06 (0.98 – 1.15)	**Infliximab 5 mg/kg**										
1.08 (1.03 – 1.14)	1.07 (1.01 – 1.13)	1.01 (0.93 – 1.08)	**Secukinumab 300 mg**									
1.22 (1.14 – 1.31)	1.20 (1.11 – 1.31)	1.13 (1.04 – 1.23)	1.12 (1.05 – 1.22)	**Ustekinumab 90 mg**								
1.23 (1.15 – 1.32)	1.21 (1.12 – 1.31)	1.14 (1.04 – 1.24)	1.13 (1.07 – 1.21)	1.01 (0.92 – 1.10)	**Secukinumab 150 mg**							
1.27 (1.18 – 1.36)	1.24 (1.17 – 1.33)	1.17 (1.06 – 1.30)	1.17 (1.08 – 1.26)	1.04 (0.94 – 1.14)	1.03 (0.94 – 1.13)	**Adalimumab 40 mg**						
1.29 (1.21 – 1.39)	1.27 (1.18 – 1.38)	1.20 (1.10 – 1.31)	1.19 (1.11 – 1.29)	1.06 (0.98 – 1.13)	1.05 (0.96 – 1.15)	1.02 (0.93 – 1.12)	**Ustekinumab 45 mg**					
1.32 (1.22 – 1.44)	1.30 (1.19 – 1.43)	1.23 (1.10 – 1.37)	1.22 (1.12 – 1.33)	1.08 (0.97 – 1.20)	1.08 (0.97 – 1.20)	1.04 (0.95 – 1.16)	1.02 (0.92 – 1.14)	**Ustekinumab 45/90 mg**				
1.75 (1.64 – 1.87)	1.72 (1.59 – 1.86)	1.62 (1.49 – 1.77)	1.61 (1.50 – 1.74)	1.43 (1.31 – 1.56)	1.43 (1.31 – 1.55)	1.38 (1.25 – 1.52)	1.36 (1.24 – 1.48)	1.33 (1.19 – 1.47)	**Etanercept 50 mg BIW**			
1.80 (1.44 – 2.40)	1.77 (1.41 – 2.37)	1.67 (1.32 – 2.23)	1.66 (1.32 – 2.21)	1.47 (1.16 – 1.97)	1.46 (1.16 – 1.96)	1.42 (1.12 – 1.91)	1.39 (1.10 – 1.87)	1.36 (1.07 – 1.83)	1.03 (0.83 – 1.35)	**Erelzi 50 mg**		
2.41 (1.95 – 3.07)	2.37 (1.92 – 3.02)	2.23 (1.78 – 2.88)	2.22 (1.79 – 2.84)	1.98 (1.58 – 2.53)	1.96 (1.57 – 2.52)	1.91 (1.54 – 2.43)	1.87 (1.50 – 2.39)	1.82 (1.45 – 2.34)	1.38 (1.11 – 1.76)	1.34 (0.94 – 1.85)	**Etanercept 50 mg QW**	
2.45 (2.02 – 3.05)	2.41 (1.98 – 3.02)	2.28 (1.86 – 2.84)	2.26 (1.86 – 2.82)	2.01 (1.65 – 2.51)	2.00 (1.64 – 2.50)	1.94 (1.58 – 2.44)	1.90 (1.56 – 2.38)	1.86 (1.50 – 2.34)	1.40 (1.16 – 1.74)	1.36 (0.98 – 1.85)	1.02 (0.75 – 1.38)	**Etanercept 25 mg BIW**
16.43 (15.95 – 16.82)	16.16 (15.50 – 16.74)	15.22 (14.18 – 16.23)	15.14 (14.47 – 15.74)	13.47 (12.51 – 14.29)	13.38 (12.46 – 14.25)	12.98 (12.16 – 13.75)	12.74 (11.86 – 13.52)	12.43 (11.39 – 13.41)	9.38 (8.77 – 10.02)	9.14 (6.84 – 11.43)	6.81 (5.36 – 8.41)	6.69 (5.38 – 8.12)	**Placebo**

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR >1 favours treatment in a given column.

f) Please produce an unadjusted NMA for the decision problem.

Results from an unadjusted NMA on the restricted network are provided as requested in Figure 13 to Figure 18.

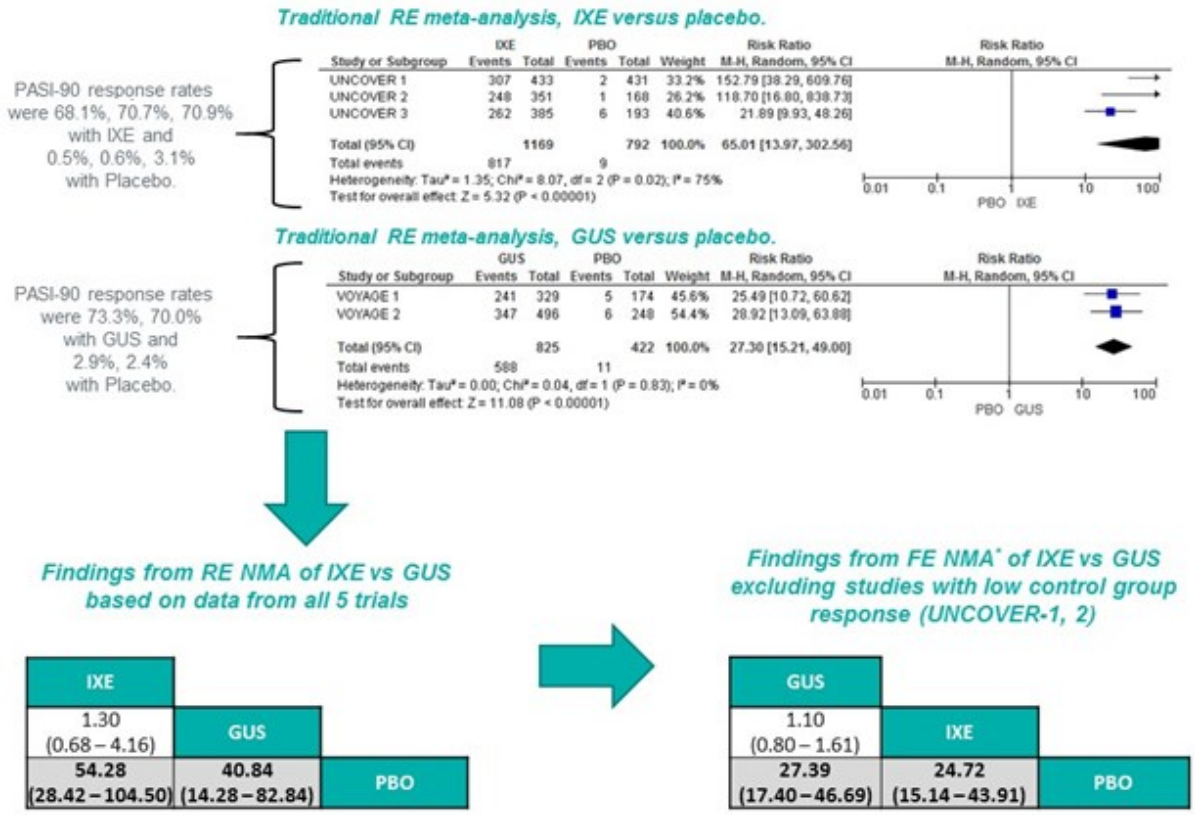
However, unadjusted results on the relative scale should be interpreted with caution. They clearly demonstrate that there was heterogeneity among comparisons within the network for PASI 90 response. Indeed, several comparisons within the network had I^2 values which exceeded 50% (see response to A6) and further inspection of this important source of heterogeneity demonstrated that low placebo group response rates among studies might be biasing effect estimates. Variations in placebo or control event rates can serve as a proxy for cumulative differences in a number of patient and study characteristics, as discussed in the company submission. Heterogeneity was identified in the placebo group event rates across studies for most PASI outcomes, as demonstrated in Figure 2 of Document B Appendix D. Even small differences in placebo response rates can have a large impact on results given placebo response is included in the denominator of relative risks and odds ratios (i.e., dividing by a small number can inflate relative effects). An example of the influence of placebo response rate on relative risks for PASI 90 was previously illustrated in Figure 5 of Document B Appendix D and demonstrates that lower placebo response is associated with more favourable results.

Ixekizumab was specifically identified as an intervention with high I^2 values. Indeed, the I^2 versus placebo was 75%, as shown in Figure 12, which represents substantial heterogeneity. It was also identified as an intervention which has low placebo response rates compared with other studies, particularly the UNCOVER 1 and UNCOVER 2 trials. Two simple Bayesian anchored indirect comparisons between guselkumab and ixekizumab were performed using placebo as the common linking intervention and using data from the guselkumab RCTs (VOYAGE 1 and VOYAGE 2) and the ixekizumab RCTs (UNCOVER 1, UNCOVER 2 and UNCOVER 3). Forest plots displaying the outcome data from these trials (along with traditional pairwise meta-analyses thereof) are presented in Figure 12**.** League tables summarising the results of the two indirect comparisons are also presented.

The first Bayesian indirect comparison was based on a random effects NMA model and incorporated data from all five studies (Figure 12); the analysis produced summary estimates that were comparable to those from the primary unadjusted NMA. However, 95% credible intervals (CrIs) were wider (relative risk [RR]: 1.30, 95% CrI 0.68-4.16). The second indirect comparison was based upon a fixed effects NMA model (due to the presence of few studies per comparison remaining) (Figure 12) and included data from only the UNCOVER 3 trial for ixekizumab and the VOYAGE 1 and 2 trials for guselkumab. This selection of studies was based on the identification of notably lower placebo group response rates in the UNCOVER 1 and UNCOVER 2 trials (0.5% and 0.6%, respectively) compared with those observed in the UNCOVER 3, VOYAGE 1, and VOYAGE 2 trials (3.1%, 2.9% and 2.4%, respectively). The objective of removing studies was to improve the homogeneity and increase the validity of the indirect comparison. The direction of the risk ratio comparing guselkumab and ixekizumab switched, and was now in favour of guselkumab (RR 1.10, 95% CrI 0.80-1.61). The change in the direction of the indirect comparison suggests there may be differences among the guselkumab and ixekizumab studies. The different results from the two simple

indirect comparisons (including vs. excluding the dissimilar UNCOVER trials) provided further support for the importance of adjusting for baseline risk in the NMAs.

Figure 12: Indirect comparison of guselkumab and ixekizumab for PASI 90 response



Key: GUS, guselkumab; IXE, ixekizumab; PBO, placebo.
Notes: Traditional meta-analyses of ixekizumab vs. placebo and guselkumab versus placebo to compare PASI 90 response are shown in forest plots along with supporting trial data. Low placebo group response rates are visible for the UNCOVER 1 and UNCOVER 2 trials for ixekizumab, while response rates in the treatment groups across trials are similar. A random effects NMA to compare ixekizumab and guselkumab using all five trials favoured ixekizumab. A sensitivity analysis using a fixed effects NMA model (to account for the low number of studies per connection in the network) and excluding UNCOVER 1 and UNCOVER 2 due to low placebo-group response rates, favoured guselkumab.

Scatterplots also demonstrated that placebo response is strongly associated with treatment effects for PASI 90 response (and other outcomes). Figure 5 of Document B Appendix D presents a series of scatterplots correlating the distribution of the covariates of interest with the treatment effects for PASI 90 response observed across studies. These scatterplots demonstrate that placebo response has the strongest relationship with treatment effect for PASI 90 response, and failure to account for this important aspect may bias estimates of comparative efficacy if there are imbalances between pairwise contrasts in the network (which there are – see Figure 2 of Document B Appendix D). This is not surprising given that placebo response is the denominator in a relative risk calculation. Also, one other covariate (biologic experience) also appears to have modest associations to treatment effects, but the association is not as strong as a placebo response. Several covariates also have

associations with placebo response, as previously illustrated in Figure 4 of Document B Appendix D.

Notably, biologic experience, and to a lesser degree mean duration of psoriasis and weight, have mild to moderate associations with placebo response. Interestingly, UNCOVER 1 has a higher percentage of patients with biologic experience compared with the VOYAGE trials (See Table 7 in Document B Appendix D). These associations suggest that placebo response may serve as a proxy for differences in both known and unknown confounders among RCTs within the evidence network. A potential known confounder could be biologic experience, while differences in standard of care across the trials impacting placebo response could be an example of an unknown confounder that may be reflected in the placebo response. Given network meta-regression analyses are limited by the number of studies in a network (and consideration of multiple covariates simultaneously would be underpowered given the evidence structure), a baseline risk-adjusted NMA, which adjusts for placebo response, can serve as an efficient meta-regression analysis to adjust for multiple known and unknown cross-trial differences among RCTs.

We, therefore, report results from the baseline-risk adjusted NMA, which accounts for differences in the placebo response, as the base case analyses. Not surprisingly, the baseline risk-adjusted model, which adjusted for differences in placebo response, was associated with the best fit among the various models considered. Criteria for selecting the best fitting model were based on NICE Guidance, and outlined *a priori* in PROSPERO:

- Review of the estimated regression coefficient and its 95% credible interval identifies the presence of a statistically significant association between the modelled variable and estimated treatment effects from the analysis.
- The estimate of the between-study standard deviation (SD) has shrunk relative to the corresponding SD estimate from the unadjusted model (suggesting there is more variation accounted for than in the unadjusted model).
- The DIC statistic from the meta-regression model is lower than the corresponding statistic from the unadjusted model by five or more points (suggesting improved model fit despite increased model complexity).
- The posterior mean of the residual deviance from the model is approximately equal to the number of intervention arms across the studies included in the NMA (suggesting the model adequately fits the data set).

The deviance information criteria (DIC) and residual deviance were assessed, as described above. However, as noted in NICE DSU TSD 3, “In deciding whether a covariate should be included, the posterior mean of the regression coefficient should be compared to the posterior standard deviation. The DIC is not a reliable criterion for deciding whether to include a covariate in random effect (RE) models. This is because RE models can fit the data equally well, whatever the between-trial variation”.

We also presented an alternative approach to adjust for cross-trial differences using risk differences, as opposed to relative effects. Rather than divide by low placebo response rates, which inflate relative effects, differences in absolute probabilities across treatments are subtracted (i.e., treated as risk differences). This may help minimize bias when there are imbalances in the number of studies with low placebo response rates across pairwise

contrasts in the network. Both the baseline-risk adjusted model and risk difference NMA's should yield less biased estimates of effect than the unadjusted NMA analyses on the relative scale reported in Figure 13 to Figure 18 below, given the issues noted previously.

Figure 13: League table summary of relative risks for the PASI 90 response at the end of induction analyses; unadjusted; restricted evidence network

Ixekizumab 80 mg Q2W												
1.05 (0.81 – 1.52)	**Infliximab 5 mg/kg**											
1.16 (1.04 – 1.33)	1.12 (0.76 – 1.47)	**Secukinumab 300 mg**										
1.26 (1.04 – 1.57)	1.21 (0.78 – 1.65)	1.08 (0.86 – 1.38)	**Guselkumab 100 mg**									
1.46 (1.23 – 1.79)	1.39 (0.94 – 1.97)	1.26 (1.03 – 1.55)	1.17 (0.89 – 1.52)	**Ustekinumab 90 mg**								
1.51 (1.28 – 1.84)	1.45 (0.96 – 2.00)	1.30 (1.17 – 1.47)	1.21 (0.90 – 1.58)	1.03 (0.82 – 1.31)	**Secukinumab 150 mg**							
1.62 (1.34 – 1.99)	1.54 (1.03 – 2.19)	1.39 (1.13 – 1.72)	1.29 (0.98 – 1.69)	1.11 (0.97 – 1.25)	1.07 (0.83 – 1.37)	**Ustekinumab 45 mg**						
1.73 (1.45 – 2.13)	1.65 (1.09 – 2.28)	1.48 (1.25 – 1.80)	1.38 (1.02 – 1.83)	1.18 (0.91 – 1.54)	1.14 (0.92 – 1.42)	1.07 (0.82 – 1.40)	**Ustekinumab 45/90 mg**					
2.11 (1.59 – 2.81)	2.02 (1.27 – 2.93)	1.81 (1.35 – 2.47)	1.68 (1.42 – 2.01)	1.44 (1.03 – 2.01)	1.40 (1.00 – 1.98)	1.30 (0.93 – 1.82)	1.22 (0.86 – 1.74)	**Adalimumab 40 mg**				
2.67 (2.25 – 3.20)	2.53 (1.72 – 3.54)	2.29 (1.90 – 2.78)	2.14 (1.55 – 2.79)	1.82 (1.48 – 2.23)	1.76 (1.44 – 2.17)	1.65 (1.33 – 2.05)	1.54 (1.21 – 1.96)	1.27 (0.87 – 1.78)	**Etanercept 50 mg BIW**			
4.82 (3.23 – 7.46)	4.52 (2.63 – 7.66)	4.13 (2.76 – 6.40)	3.83 (2.38 – 6.27)	3.29 (2.17 – 5.08)	3.19 (2.10 – 4.95)	2.98 (1.95 – 4.63)	2.79 (1.79 – 4.38)	2.28 (1.36 – 3.88)	1.81 (1.26 – 2.67)	**Etanercept 25 mg BIW**		
7.07 (4.12 – 12.28)	6.68 (3.52 – 12.45)	6.07 (3.51 – 10.62)	5.61 (3.08 – 10.14)	4.80 (2.78 – 8.42)	4.66 (2.69 – 8.28)	4.33 (2.51 – 7.62)	4.07 (2.32 – 7.26)	3.35 (1.77 – 6.22)	2.64 (1.59 – 4.50)	1.45 (0.76 – 2.79)	**Etanercept 50 mg QW**	
44.28 (40.26 – 47.96)	42.51 (28.62 – 54.71)	37.92 (32.83 – 42.73)	35.23 (28.73 – 41.66)	30.11 (24.52 – 36.08)	29.24 (23.64 – 35.20)	27.27 (22.00 – 33.09)	25.60 (20.31 – 31.17)	20.88 (15.98 – 27.30)	16.53 (13.24 – 20.59)	9.20 (5.78 – 13.94)	6.27 (3.55 – 10.90)	**Placebo**

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR >1 favours treatment in a given column.

Figure 14: League table summary of relative risks for the PASI 90 response at the end of induction analyses; unadjusted; restricted evidence network

Infliximab 5 mg/kg												
1.01 (0.94 – 1.06)	**Ixekizumab 80 mg Q2W**											
1.07 (0.98 – 1.16)	1.06 (1.00 – 1.14)	**Guselkumab 100 mg**										
1.09 (1.01 – 1.16)	1.08 (1.03 – 1.14)	1.02 (0.94 – 1.09)	**Secukinumab 300 mg**									
1.22 (1.11 – 1.32)	1.21 (1.13 – 1.30)	1.14 (1.04 – 1.24)	1.12 (1.04 – 1.21)	**Ustekinumab 90 mg**								
1.21 (1.11 – 1.32)	1.20 (1.12 – 1.30)	1.14 (1.03 – 1.24)	1.12 (1.06 – 1.18)	1.00 (0.90 – 1.09)	**Secukinumab 150 mg**							
1.31 (1.18 – 1.43)	1.30 (1.20 – 1.41)	1.23 (1.10 – 1.35)	1.20 (1.10 – 1.32)	1.08 (1.01 – 1.15)	1.08 (0.97 – 1.20)	**Ustekinumab 45 mg**						
1.38 (1.24 – 1.54)	1.37 (1.25 – 1.52)	1.29 (1.15 – 1.45)	1.27 (1.15 – 1.41)	1.14 (1.01 – 1.28)	1.14 (1.02 – 1.28)	1.06 (0.94 – 1.20)	**Ustekinumab 45/90 mg**					
1.43 (1.27 – 1.60)	1.41 (1.28 – 1.58)	1.33 (1.23 – 1.45)	1.31 (1.18 – 1.47)	1.17 (1.04 – 1.33)	1.17 (1.04 – 1.33)	1.08 (0.96 – 1.25)	1.03 (0.90 – 1.19)	**Adalimumab 40 mg**				
1.69 (1.53 – 1.85)	1.68 (1.56 – 1.82)	1.58 (1.42 – 1.75)	1.55 (1.44 – 1.69)	1.39 (1.27 – 1.52)	1.39 (1.27 – 1.53)	1.29 (1.17 – 1.43)	1.22 (1.08 – 1.38)	1.18 (1.04 – 1.36)	**Etanercept 50 mg BIW**			
1.73 (1.40 – 2.24)	1.72 (1.41 – 2.23)	1.61 (1.32 – 2.11)	1.59 (1.30 – 2.06)	1.42 (1.15 – 1.85)	1.42 (1.17 – 1.86)	1.32 (1.08 – 1.72)	1.25 (1.00 – 1.65)	1.22 (0.97 – 1.61)	1.02 (0.85 – 1.30)	**Erelzi 50 mg**		
2.31 (1.86 – 2.89)	2.30 (1.84 – 2.85)	2.17 (1.72 – 2.71)	2.13 (1.68 – 2.66)	1.90 (1.48 – 2.38)	1.91 (1.48 – 2.39)	1.78 (1.37 – 2.22)	1.67 (1.33 – 2.12)	1.63 (1.26 – 2.06)	1.37 (1.10 – 1.68)	1.33 (0.98 – 1.79)	**Etanercept 25 mg BIW**	
2.84 (2.16 – 3.95)	2.84 (2.15 – 3.92)	2.67 (2.01 – 3.71)	2.63 (1.99 – 3.64)	2.34 (1.77 – 3.28)	2.36 (1.78 – 3.26)	2.18 (1.65 – 3.05)	2.07 (1.54 – 2.91)	2.01 (1.49 – 2.81)	1.69 (1.30 – 2.31)	1.64 (1.16 – 2.36)	1.23 (0.87 – 1.84)	**Etanercept 50 mg QW**
16.74 (15.63 – 17.50)	16.62 (16.13 – 17.00)	15.65 (14.70 – 16.39)	15.35 (14.64 – 16.09)	13.72 (12.78 – 14.70)	13.78 (12.77 – 14.77)	12.74 (11.75 – 13.85)	12.10 (10.91 – 13.31)	11.74 (10.57 – 12.91)	9.91 (9.06 – 10.73)	9.68 (7.43 – 11.81)	7.21 (5.78 – 9.08)	5.85 (4.23 – 7.73)	**Placebo**

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR >1 favours treatment in a given column.

Figure 15: League table summary of relative risks for the AE rate at the end of induction analyses; unadjusted; restricted evidence network

Placebo											
0.98 (0.90 – 1.07)	Ustekinumab 90 mg										
1.01 (0.83 – 1.26)	1.03 (0.84 – 1.28)	Etanercept 50 mg QW									
0.93 (0.84 – 1.03)	0.94 (0.84 – 1.08)	0.92 (0.73 – 1.14)	Guselkumab 100 mg								
0.93 (0.86 – 1.00)	0.94 (0.86 – 1.02)	0.92 (0.73 – 1.12)	1.00 (0.88 – 1.13)	Ustekinumab 45 mg							
0.91 (0.85 – 0.99)	0.93 (0.84 – 1.04)	0.91 (0.72 – 1.11)	0.98 (0.89 – 1.08)	0.98 (0.89 – 1.10)	Adalimumab 40 mg						
0.90 (0.83 – 0.98)	0.92 (0.81 – 1.03)	0.89 (0.70 – 1.11)	0.97 (0.84 – 1.10)	0.97 (0.87 – 1.09)	0.99 (0.88 – 1.09)	Ustekinumab 45/90 mg					
0.89 (0.84 – 0.95)	0.91 (0.82 – 1.00)	0.89 (0.71 – 1.06)	0.96 (0.85 – 1.08)	0.96 (0.88 – 1.06)	0.97 (0.89 – 1.07)	0.99 (0.89 – 1.09)	Etanercept 50 mg BIW				
0.86 (0.80 – 0.92)	0.88 (0.78 – 0.97)	0.85 (0.68 – 1.03)	0.93 (0.81 – 1.04)	0.93 (0.84 – 1.03)	0.94 (0.85 – 1.04)	0.95 (0.87 – 1.05)	0.96 (0.88 – 1.05)	Secukinumab 300 mg			
0.84 (0.79 – 0.90)	0.85 (0.77 – 0.95)	0.83 (0.67 – 1.01)	0.90 (0.79 – 1.02)	0.91 (0.82 – 1.00)	0.92 (0.83 – 1.01)	0.93 (0.84 – 1.03)	0.94 (0.87 – 1.01)	0.98 (0.89 – 1.08)	Ixekizumab 80 mg Q2W		
0.83 (0.78 – 0.90)	0.85 (0.76 – 0.95)	0.83 (0.66 – 1.00)	0.90 (0.79 – 1.01)	0.90 (0.82 – 1.01)	0.92 (0.82 – 1.02)	0.93 (0.83 – 1.03)	0.94 (0.86 – 1.03)	0.97 (0.91 – 1.04)	1.00 (0.90 – 1.10)	Secukinumab 150 mg	
0.77 (0.71 – 0.87)	0.79 (0.69 – 0.92)	0.77 (0.61 – 0.96)	0.84 (0.72 – 0.97)	0.84 (0.74 – 0.96)	0.85 (0.75 – 0.97)	0.86 (0.76 – 0.99)	0.87 (0.78 – 0.98)	0.90 (0.81 – 1.04)	0.93 (0.81 – 1.06)	0.93 (0.83 – 1.06)	Infliximab 5 mg/kg

Key: AE, adverse event; BIW, biweekly; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR <1 favours treatment in a given column.

Figure 16: League table summary of relative differences for the PASI 90 response at the end of induction analyses; unadjusted; restricted evidence network

Ixekizumab 80 mg Q2W												
0.75 (-8.44 to 9.95)	**Guselkumab 100 mg**											
12.21 (4.43 to 19.89)	11.44 (2.30 to 20.54)	**Secukinumab 300 mg**										
18.92 (10.62 to 27.28)	18.21 (8.56 to 27.85)	6.73 (-1.66 to 15.07)	**Infliximab 5 mg/kg**									
24.29 (16.80 to 31.87)	23.54 (15.84 to 31.26)	12.06 (4.72 to 19.59)	5.34 (-2.76 to 13.50)	**Adalimumab 40 mg**								
25.04 (16.82 to 33.22)	24.28 (14.73 to 33.79)	12.84 (4.67 to 20.96)	6.12 (-2.69 to 14.74)	0.76 (-7.27 to 8.58)	**Ustekinumab 90 mg**							
26.28 (18.69 to 33.89)	25.53 (16.52 to 34.53)	14.06 (6.47 to 21.62)	7.34 (-0.83 to 15.52)	2.00 (-5.39 to 9.31)	1.25 (-5.37 to 7.86)	**Ustekinumab 45 mg**						
27.28 (19.71 to 35.06)	26.56 (16.86 to 36.27)	15.06 (7.83 to 22.53)	8.35 (-0.41 to 17.37)	3.02 (-5.12 to 11.12)	2.25 (-6.35 to 11.07)	1.03 (-7.07 to 9.29)	**Ustekinumab 45/90 mg**					
28.36 (20.30 to 36.34)	27.61 (18.16 to 37.03)	16.13 (9.96 to 22.26)	9.41 (0.87 to 18.00)	4.07 (-3.82 to 11.80)	3.30 (-5.02 to 11.74)	2.09 (-5.80 to 9.94)	1.05 (-7.18 to 9.21)	**Secukinumab 150 mg**				
47.55 (41.53 to 53.54)	46.82 (38.76 to 54.67)	35.34 (29.18 to 41.43)	28.61 (21.65 to 35.53)	23.27 (17.14 to 29.18)	22.51 (16.02 to 28.97)	21.27 (15.45 to 27.09)	20.25 (13.26 to 27.10)	19.20 (12.70 to 25.68)	**Etanercept 50 mg BIW**			
58.61 (49.57 to 67.54)	57.88 (47.53 to 68.13)	46.38 (37.39 to 55.34)	39.65 (30.18 to 49.14)	34.31 (25.43 to 43.02)	33.55 (24.36 to 42.84)	32.32 (23.53 to 41.12)	31.30 (21.79 to 40.68)	30.24 (21.06 to 39.47)	11.04 (3.71 to 18.39)	**Etanercept 25 mg BIW**		
58.89 (49.38 to 68.33)	58.14 (47.49 to 68.72)	46.66 (37.26 to 56.04)	39.96 (30.00 to 49.85)	34.59 (25.23 to 43.78)	33.84 (24.09 to 43.48)	32.63 (23.28 to 41.98)	31.56 (21.58 to 41.38)	30.53 (20.92 to 40.14)	11.35 (3.40 to 19.33)	0.29 (-10.12 to 10.65)	**Etanercept 50 mg QW**	
69.50 (63.94 to 75.16)	68.76 (61.41 to 76.06)	57.29 (51.78 to 62.83)	50.57 (44.29 to 56.86)	45.23 (40.08 to 50.28)	44.48 (38.45 to 50.55)	43.22 (38.02 to 48.51)	42.19 (35.85 to 48.47)	41.14 (35.26 to 47.08)	21.96 (18.76 to 25.25)	10.92 (3.80 to 18.09)	10.63 (2.91 to 18.35)	**Placebo**

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; RD, risk difference; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RD%s and 95% CrIs. A RD% >0 favours treatment in a given column.

Figure 17: League table summary of relative differences for the PASI 75 response at the end of induction analyses; unadjusted; restricted evidence network

Ixekizumab 80 mg Q2W													
2.87 (-3.75 to 9.51)	Guselkumab 100 mg												
8.45 (2.12 to 14.63)	5.59 (-1.78 to 12.60)	Infliximab 5 mg/kg											
9.04 (3.38 to 14.40)	6.16 (-0.62 to 12.60)	0.56 (-5.77 to 6.87)	Secukinumab 300 mg										
17.46 (11.47 to 23.26)	14.57 (7.52 to 21.47)	8.97 (2.39 to 15.66)	8.42 (3.89 to 13.07)	Secukinumab 150 mg									
18.23 (12.24 to 24.33)	15.33 (8.31 to 22.49)	9.76 (3.21 to 16.75)	9.19 (3.25 to 15.57)	0.76 (-5.54 to 7.40)	Ustekinumab 90 mg								
20.69 (15.12 to 26.36)	17.81 (11.93 to 23.72)	12.24 (6.01 to 18.66)	11.67 (6.13 to 17.50)	3.22 (-2.71 to 9.40)	2.48 (-3.73 to 8.55)	Adalimumab 40 mg							
21.41 (15.70 to 26.92)	18.53 (11.42 to 25.46)	12.94 (6.26 to 19.71)	12.38 (7.17 to 17.78)	3.95 (-2.15 to 10.09)	3.20 (-3.60 to 9.56)	0.71 (-5.51 to 6.82)	Ustekinumab 45/90 mg						
22.15 (16.40 to 27.89)	19.26 (12.52 to 26.12)	13.70 (7.34 to 20.38)	13.14 (7.50 to 19.13)	4.72 (-1.43 to 10.97)	3.94 (-1.47 to 9.26)	1.45 (-4.34 to 7.32)	0.75 (-5.44 to 7.11)	Ustekinumab 45 mg					
40.09 (35.58 to 44.56)	37.21 (31.21 to 43.12)	31.61 (26.25 to 37.28)	31.06 (26.42 to 35.91)	22.62 (17.56 to 27.85)	21.86 (16.71 to 26.82)	19.39 (14.49 to 24.23)	18.68 (13.44 to 24.05)	17.92 (13.10 to 22.67)	Etanercept 50 mg BIW				
41.24 (30.24 to 52.03)	38.34 (26.68 to 49.78)	32.78 (21.39 to 44.18)	32.21 (21.22 to 43.20)	23.81 (12.55 to 34.88)	22.99 (11.76 to 34.05)	20.54 (9.45 to 31.46)	19.80 (8.55 to 31.06)	19.07 (8.00 to 30.00)	1.17 (-8.87 to 11.02)	Erelzi 50 mg			
54.35 (45.77 to 62.88)	51.46 (42.19 to 60.80)	45.93 (36.85 to 55.04)	45.35 (36.74 to 54.10)	36.94 (27.99 to 45.81)	36.16 (27.14 to 44.98)	33.69 (24.90 to 42.37)	32.97 (23.97 to 41.92)	32.20 (23.49 to 40.92)	14.29 (6.37 to 22.18)	13.19 (0.38 to 25.81)	Etanercept 50 mg QW		
54.38 (46.78 to 62.24)	51.46 (43.00 to 60.19)	45.92 (37.69 to 54.39)	45.35 (37.65 to 53.51)	36.91 (29.01 to 45.28)	36.13 (28.06 to 44.48)	33.70 (25.88 to 41.65)	32.99 (24.89 to 41.36)	32.25 (24.37 to 40.25)	14.29 (7.43 to 21.49)	13.15 (1.13 to 25.63)	0.00 (-10.05 to 10.47)	Etanercept 25 mg BIW	
84.71 (80.74 to 88.61)	81.83 (76.49 to 87.11)	76.26 (71.46 to 81.20)	75.67 (71.74 to 79.84)	67.25 (62.76 to 71.82)	66.48 (61.75 to 71.04)	64.00 (59.92 to 68.00)	63.29 (58.70 to 68.00)	62.56 (58.28 to 66.74)	44.63 (41.86 to 47.34)	43.45 (33.24 to 53.82)	30.33 (22.65 to 38.08)	30.34 (23.45 to 36.97)	Placebo

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; RD, risk difference; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RD%s and 95% CrIs. A RD% >0 favours treatment in a given column.

Figure 18: League table summary of relative differences for the AE rate at the end of induction analyses; unadjusted; restricted evidence network

Placebo											
-1.80 (-7.18 to 3.41)	Ustekinumab 90 mg										
-1.17 (-10.18 to 8.38)	0.85 (-9.41 to 11.19)	Etanercept 50 mg QW									
-2.53 (-8.88 to 3.36)	-0.83 (-8.39 to 7.62)	-1.18 (-12.56 to 8.82)	Guselkumab 100 mg								
-3.84 (-8.18 to 0.38)	-2.15 (-8.51 to 4.21)	-2.57 (-12.94 to 6.91)	-1.30 (-8.62 to 6.01)	Ustekinumab 45 mg							
-4.05 (-8.03 to -0.09)	-2.40 (-8.38 to 4.68)	-2.89 (-13.26 to 6.83)	-1.34 (-8.18 to 5.68)	-0.14 (-6.19 to 5.72)	Adalimumab 40 mg						
-6.75 (-11.23 to -2.06)	-4.94 (-11.57 to 1.67)	-5.55 (-16.24 to 4.23)	-4.22 (-12.29 to 3.68)	-2.92 (-8.86 to 3.52)	-2.76 (-8.47 to 3.32)	Ustekinumab 45/90 mg					
-6.76 (-9.72 to -3.72)	-4.95 (-9.89 to 0.37)	-5.54 (-14.96 to 3.25)	-4.18 (-10.81 to 2.66)	-2.91 (-7.76 to 2.01)	-2.62 (-7.71 to 2.36)	0.09 (-5.63 to 5.35)	Etanercept 50 mg BIW				
-9.17 (-14.42 to -4.18)	-7.59 (-14.58 to -0.26)	-7.99 (-19.07 to 2.08)	-6.83 (-14.43 to 1.43)	-5.48 (-11.92 to 1.21)	-5.26 (-11.66 to 1.26)	-2.43 (-9.37 to 4.65)	-2.42 (-8.13 to 2.90)	Infliximab 5 mg/kg			
-9.28 (-13.78 to -5.24)	-7.61 (-13.98 to -0.53)	-8.31 (-18.38 to 1.56)	-6.63 (-14.75 to 0.62)	-5.50 (-11.29 to 0.41)	-5.35 (-11.25 to 0.42)	-2.56 (-8.14 to 2.85)	-2.48 (-8.04 to 2.41)	0.05 (-6.98 to 6.50)	Secukinumab 300 mg		
-10.10 (-14.39 to -5.64)	-8.35 (-14.71 to -1.69)	-8.90 (-19.66 to 0.99)	-7.70 (-14.89 to 0.32)	-6.22 (-12.17 to 0.08)	-6.03 (-11.80 to 0.01)	-3.34 (-9.10 to 2.46)	-3.39 (-8.55 to 1.92)	-0.95 (-7.53 to 5.88)	-0.82 (-6.55 to 5.10)	Ixekizumab 80 mg Q2W	
-10.35 (-14.85 to -5.78)	-8.64 (-15.30 to -1.28)	-9.08 (-19.86 to 0.77)	-7.74 (-15.88 to -0.13)	-6.49 (-12.36 to -0.26)	-6.41 (-12.23 to -0.10)	-3.64 (-9.67 to 2.33)	-3.65 (-8.84 to 1.65)	-0.99 (-8.03 to 5.74)	-1.01 (-5.78 to 3.90)	-0.24 (-6.68 to 6.01)	Secukinumab 150 mg

Key: AE, adverse event; BIW, biweekly; RD, risk difference; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RD%s and 95% CrIs. A RD <0 favours treatment in a given column.

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g) Please reproduce the NMA and pairwise comparisons on safety including the safety from 'as-treated' population of NAVIGATE.

The NMA focuses on the induction or placebo-controlled period for up to 16 weeks. The NAVIGATE trial consisted of a 16-week open-label period where all patients received open-label ustekinumab. At Week 16, patients were randomised based on their response to ustekinumab. Given all patients received ustekinumab up to week 16 and were randomised based on their response to ustekinumab, we are not able to incorporate data from NAVIGATE into the induction NMA; that is, no comparative induction data are available to connect to the NAVIGATE trial to the network.

Please refer to question A17 for the full adverse events breakdown requested by e-mail on the 22 November.

h) Please produce an NMA adjusted for both baseline risk and duration of psoriasis.

An NMA adjusted for both baseline risk and duration of psoriasis has been conducted on the full evidence network and the restricted network. Outcomes of these analyses are provided in
Figure 19 to Figure 22. Similar to findings reported from other NMAs, guselkumab demonstrates comparable or greater efficacy compared with alternative biologics at the end of induction when adjusting for both baseline risk and duration of psoriasis.

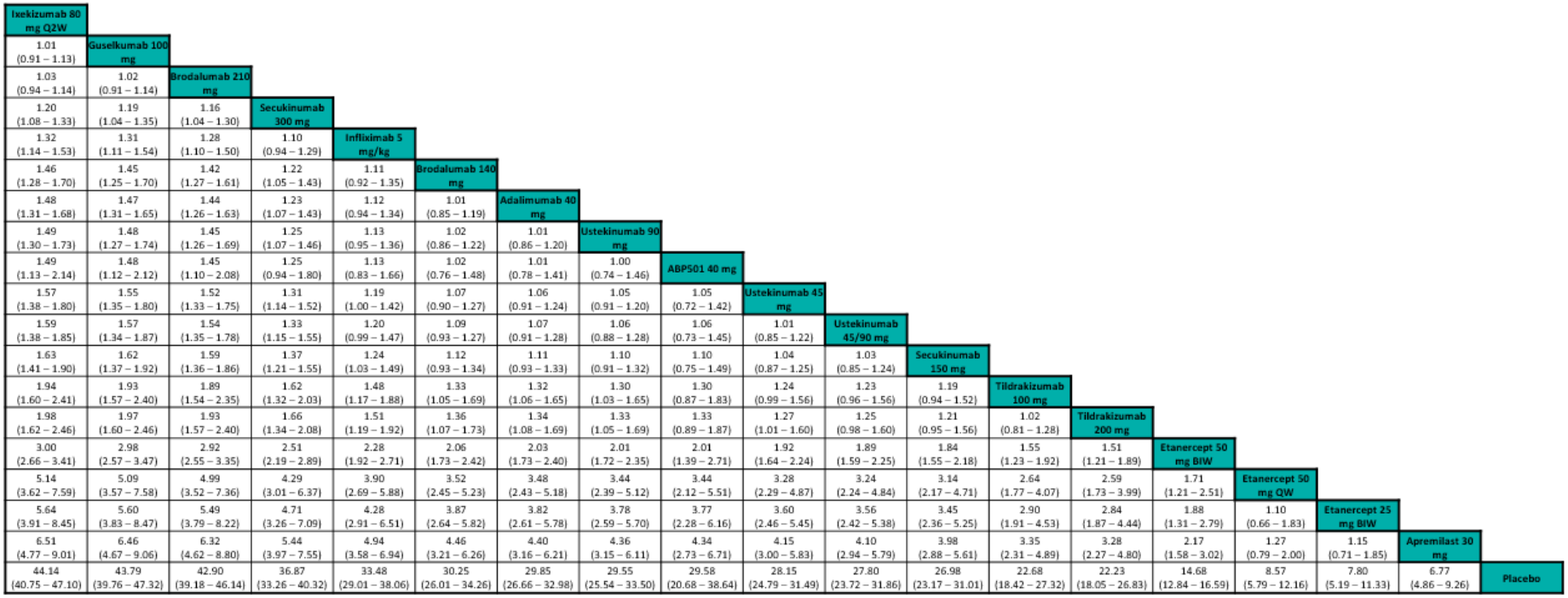
Model fit statistics are summarised in Table 10.

Table 10: Summary of model fit statistics

	PASI 90	**PASI 75**
Baseline risk Adjusted and Duration of Psoriasis NMA – Restricted Network	Beta[Baseline-risk]: -0.96 (-1.08 to -0.81) Beta[Duration of Psoriasis]: -0.04 (-0.01 to 0.02) SD: 0.18 (0.01 to 0.02) DIC: 581.47 Resdev: 96.25 vs. 93 data points	Beta[Baseline-risk]: -0.73 (-0.93 to -0.48) Beta[Duration of Psoriasis]: 0.01 (-0.04 to 0.07) SD: 0.15 (0.02 to 0.26) DIC: 618.40 Resdev: 95.30 vs. 95 data points
Baseline risk Adjusted and Duration of Psoriasis NMA – Full Network	Beta[Baseline-risk]: -0.97 (-1.08 to -0.85) Beta[Duration of Psoriasis]: -0.04 (-0.09 to 0.01) SD: 0.19 (0.12 to 0.27) DIC: 718.38	Beta[Baseline-risk]: -0.73 (-0.90 to -0.53) Beta[Duration of Psoriasis]: 0.01 (-0.03 to 0.06) SD: 0.12 (0.01 to 0.21) DIC: 717.59

	Resdev: 116.86 vs. 112 data points	Resdev: 115.18 vs. 114 data points
Baseline-risk Adjusted NMA – Restricted Network	Beta: -0.94 (-1.06 to -0.78) SD: 0.12 (0.07 to 0.32) DIC: 559.24 Resdev: 95.01 vs. 93 data points	Beta: -0.74 (-0.94 to -0.52) SD: 0.15 (0.03 to 0.25) DIC: 618.44 Resdev: 95.88 vs. 95 data points
Baseline-risk Adjusted NMA – Full Network	Beta: -0.95 (-1.05 to -0.83) SD: 0.09 (0.03 to 0.21) DIC: 689.21 Resdev: 109.12 vs. 112 data points	Beta: -0.74 (-0.91 to -0.55) SD: 0.12 (0.02 to 0.21) DIC: 753.22 Resdev: 115.51 vs. 114 data points
Key: DIC, deviance information criteria; NMA, network meta-analysis; Resdev, residual deviance; SD, standard deviation.		

Figure 19: League table summary of relative risks for the PASI 90 response at the end of induction analyses; baseline risk and duration of psoriasis-adjusted; full evidence network



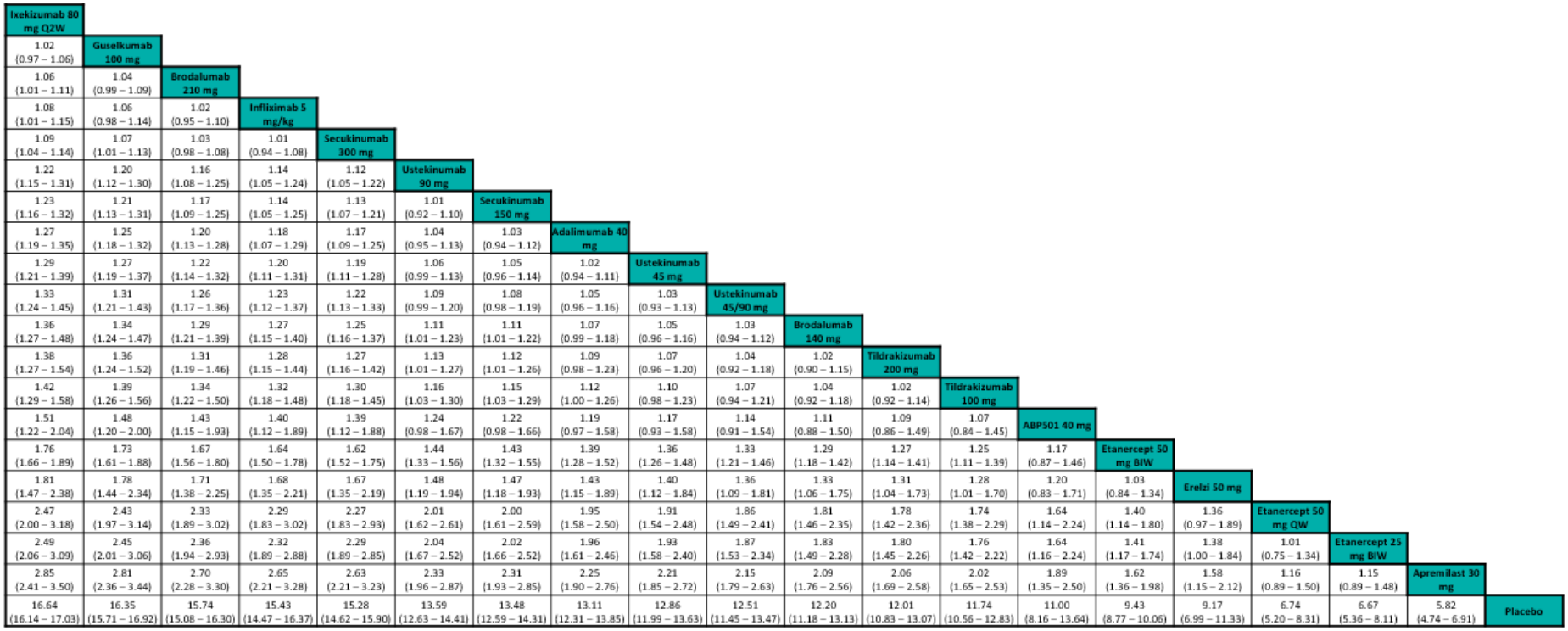
Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR >1 favours treatment in a given column.

Figure 20: League table summary of relative risks for the PASI 90 response at the end of induction analyses; baseline risk and duration of psoriasis-adjusted; restricted evidence network

Ixekizumab 80 mg Q2W												
1.01 (0.90 – 1.15)	**Guselkumab 100 mg**											
1.20 (1.07 – 1.35)	1.18 (1.02 – 1.36)	**Secukinumab 300 mg**										
1.32 (1.13 – 1.56)	1.30 (1.08 – 1.57)	1.10 (0.93 – 1.31)	**Infliximab 5 mg/kg**									
1.49 (1.30 – 1.73)	1.48 (1.30 – 1.68)	1.25 (1.06 – 1.46)	1.13 (0.93 – 1.39)	**Adalimumab 40 mg**								
1.50 (1.29 – 1.77)	1.48 (1.25 – 1.78)	1.25 (1.06 – 1.49)	1.14 (0.93 – 1.40)	1.00 (0.83 – 1.21)	**Ustekinumab 90 mg**							
1.58 (1.37 – 1.83)	1.56 (1.33 – 1.84)	1.32 (1.13 – 1.56)	1.20 (0.99 – 1.45)	1.06 (0.89 – 1.26)	1.05 (0.90 – 1.22)	**Ustekinumab 45 mg**						
1.60 (1.38 – 1.90)	1.58 (1.33 – 1.92)	1.34 (1.14 – 1.59)	1.22 (0.98 – 1.52)	1.07 (0.89 – 1.31)	1.07 (0.87 – 1.32)	1.02 (0.83 – 1.25)	**Ustekinumab 45/90 mg**					
1.64 (1.40 – 1.93)	1.62 (1.35 – 1.95)	1.37 (1.20 – 1.57)	1.24 (1.01 – 1.52)	1.10 (0.90 – 1.34)	1.09 (0.89 – 1.33)	1.04 (0.85 – 1.26)	1.02 (0.83 – 1.25)	**Secukinumab 150 mg**				
3.01 (2.64 – 3.45)	2.98 (2.51 – 3.51)	2.51 (2.16 – 2.93)	2.28 (1.89 – 2.75)	2.01 (1.68 – 2.41)	2.01 (1.68 – 2.38)	1.91 (1.60 – 2.26)	1.88 (1.53 – 2.27)	1.84 (1.53 – 2.21)	**Etanercept 50 mg BIW**			
5.16 (3.57 – 7.70)	5.10 (3.51 – 7.67)	4.31 (2.96 – 6.48)	3.92 (2.64 – 5.98)	3.45 (2.36 – 5.22)	3.44 (2.33 – 5.20)	3.27 (2.22 – 4.93)	3.21 (2.17 – 4.88)	3.15 (2.13 – 4.80)	1.71 (1.19 – 2.56)	**Etanercept 50 mg QW**		
5.67 (3.87 – 8.56)	5.61 (3.77 – 8.55)	4.73 (3.22 – 7.19)	4.30 (2.87 – 6.64)	3.79 (2.53 – 5.85)	3.78 (2.53 – 5.79)	3.59 (2.41 – 5.50)	3.53 (2.35 – 5.44)	3.46 (2.32 – 5.34)	1.88 (1.29 – 2.83)	1.10 (0.64 – 1.88)	**Etanercept 25 mg BIW**	
42.09 (38.68 – 45.16)	41.61 (37.41 – 45.25)	35.12 (31.39 – 38.70)	31.91 (27.19 – 36.89)	28.16 (24.90 – 31.36)	28.05 (23.96 – 32.15)	26.64 (23.21 – 30.09)	26.22 (22.07 – 30.42)	25.70 (21.78 – 29.82)	13.96 (12.15 – 15.95)	8.14 (5.46 – 11.74)	7.42 (4.88 – 10.87)	**Placebo**

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR >1 favours treatment in a given column.

Figure 21: League table summary of relative risks for the PASI 75 response at the end of induction analyses; baseline risk and duration of psoriasis-adjusted; full evidence network



Ixekizumab 80 mg Q2W																		
1.02 (0.97 – 1.06)	Guselkumab 100 mg																	
1.06 (1.01 – 1.11)	1.04 (0.99 – 1.09)	Brodalumab 210 mg																
1.08 (1.01 – 1.15)	1.06 (0.98 – 1.14)	1.02 (0.95 – 1.10)	Infliximab 5 mg/kg															
1.09 (1.04 – 1.14)	1.07 (1.01 – 1.13)	1.03 (0.98 – 1.08)	1.01 (0.94 – 1.08)	Secukinumab 300 mg														
1.22 (1.15 – 1.31)	1.20 (1.12 – 1.30)	1.16 (1.08 – 1.25)	1.14 (1.05 – 1.24)	1.12 (1.05 – 1.22)	Ustekinumab 90 mg													
1.23 (1.16 – 1.32)	1.21 (1.13 – 1.31)	1.17 (1.09 – 1.25)	1.14 (1.05 – 1.25)	1.13 (1.07 – 1.21)	1.01 (0.92 – 1.10)	Secukinumab 150 mg												
1.27 (1.19 – 1.35)	1.25 (1.18 – 1.32)	1.20 (1.13 – 1.28)	1.18 (1.07 – 1.29)	1.17 (1.09 – 1.25)	1.04 (0.95 – 1.13)	1.03 (0.94 – 1.12)	Adalimumab 40 mg											
1.29 (1.21 – 1.39)	1.27 (1.19 – 1.37)	1.22 (1.14 – 1.32)	1.20 (1.11 – 1.31)	1.19 (1.11 – 1.28)	1.06 (0.99 – 1.13)	1.05 (0.96 – 1.14)	1.02 (0.94 – 1.11)	Ustekinumab 45 mg										
1.33 (1.24 – 1.45)	1.31 (1.21 – 1.43)	1.26 (1.17 – 1.36)	1.23 (1.12 – 1.37)	1.22 (1.13 – 1.33)	1.09 (0.99 – 1.20)	1.08 (0.98 – 1.19)	1.05 (0.96 – 1.16)	1.03 (0.93 – 1.13)	Ustekinumab 45/90 mg									
1.36 (1.27 – 1.48)	1.34 (1.24 – 1.47)	1.29 (1.21 – 1.39)	1.27 (1.15 – 1.40)	1.25 (1.16 – 1.37)	1.11 (1.01 – 1.23)	1.11 (1.01 – 1.22)	1.07 (0.99 – 1.18)	1.05 (0.96 – 1.16)	1.03 (0.94 – 1.12)	Brodalumab 140 mg								
1.38 (1.27 – 1.54)	1.36 (1.24 – 1.52)	1.31 (1.19 – 1.46)	1.28 (1.15 – 1.44)	1.27 (1.16 – 1.42)	1.13 (1.01 – 1.27)	1.12 (1.01 – 1.26)	1.09 (0.98 – 1.23)	1.07 (0.96 – 1.20)	1.04 (0.92 – 1.18)	1.02 (0.90 – 1.15)	Tildrakizumab 200 mg							
1.42 (1.29 – 1.58)	1.39 (1.26 – 1.56)	1.34 (1.22 – 1.50)	1.32 (1.18 – 1.48)	1.30 (1.18 – 1.45)	1.16 (1.03 – 1.30)	1.15 (1.03 – 1.29)	1.12 (1.00 – 1.26)	1.10 (0.98 – 1.23)	1.07 (0.94 – 1.21)	1.04 (0.92 – 1.18)	1.02 (0.92 – 1.14)	Tildrakizumab 100 mg						
1.51 (1.22 – 2.04)	1.48 (1.20 – 2.00)	1.43 (1.15 – 1.93)	1.40 (1.12 – 1.89)	1.39 (1.12 – 1.88)	1.24 (0.98 – 1.67)	1.22 (0.98 – 1.66)	1.19 (0.97 – 1.58)	1.17 (0.93 – 1.58)	1.14 (0.91 – 1.54)	1.11 (0.88 – 1.50)	1.09 (0.86 – 1.49)	1.07 (0.84 – 1.45)	ABP501 40 mg					
1.76 (1.66 – 1.89)	1.73 (1.61 – 1.88)	1.67 (1.56 – 1.80)	1.64 (1.50 – 1.78)	1.62 (1.52 – 1.75)	1.44 (1.33 – 1.56)	1.43 (1.32 – 1.55)	1.39 (1.28 – 1.52)	1.36 (1.26 – 1.48)	1.33 (1.21 – 1.46)	1.29 (1.18 – 1.42)	1.27 (1.14 – 1.41)	1.25 (1.11 – 1.39)	1.17 (0.87 – 1.46)	Etanercept 50 mg BIW				
1.81 (1.47 – 2.38)	1.78 (1.44 – 2.34)	1.71 (1.38 – 2.25)	1.68 (1.35 – 2.21)	1.67 (1.35 – 2.19)	1.48 (1.19 – 1.94)	1.47 (1.18 – 1.93)	1.43 (1.15 – 1.89)	1.40 (1.12 – 1.84)	1.36 (1.09 – 1.81)	1.33 (1.06 – 1.75)	1.31 (1.04 – 1.73)	1.28 (1.01 – 1.70)	1.20 (0.83 – 1.71)	1.03 (0.84 – 1.34)	Erelzi 50 mg			
2.47 (2.00 – 3.18)	2.43 (1.97 – 3.14)	2.33 (1.89 – 3.02)	2.29 (1.83 – 3.02)	2.27 (1.83 – 2.93)	2.01 (1.62 – 2.61)	2.00 (1.61 – 2.59)	1.95 (1.58 – 2.50)	1.91 (1.54 – 2.48)	1.86 (1.49 – 2.41)	1.81 (1.46 – 2.35)	1.78 (1.42 – 2.36)	1.74 (1.38 – 2.29)	1.64 (1.14 – 2.24)	1.40 (1.14 – 1.80)	1.36 (0.97 – 1.89)	Etanercept 50 mg QW		
2.49 (2.06 – 3.09)	2.45 (2.01 – 3.06)	2.36 (1.94 – 2.93)	2.32 (1.89 – 2.88)	2.29 (1.89 – 2.85)	2.04 (1.67 – 2.52)	2.02 (1.66 – 2.52)	1.96 (1.61 – 2.46)	1.93 (1.58 – 2.40)	1.87 (1.53 – 2.34)	1.83 (1.49 – 2.28)	1.80 (1.45 – 2.26)	1.76 (1.42 – 2.22)	1.64 (1.16 – 2.24)	1.41 (1.17 – 1.74)	1.38 (1.00 – 1.84)	1.01 (0.75 – 1.34)	Etanercept 25 mg BIW	
2.85 (2.41 – 3.50)	2.81 (2.36 – 3.44)	2.70 (2.28 – 3.30)	2.65 (2.21 – 3.28)	2.63 (2.21 – 3.23)	2.33 (1.96 – 2.87)	2.31 (1.93 – 2.85)	2.25 (1.90 – 2.76)	2.21 (1.85 – 2.72)	2.15 (1.79 – 2.63)	2.09 (1.76 – 2.56)	2.06 (1.69 – 2.58)	2.02 (1.65 – 2.53)	1.89 (1.35 – 2.50)	1.62 (1.36 – 1.98)	1.58 (1.15 – 2.12)	1.16 (0.89 – 1.50)	1.15 (0.89 – 1.48)	Apremilast 30 mg
16.64 (16.14 – 17.03)	16.35 (15.71 – 16.92)	15.74 (15.08 – 16.30)	15.43 (14.47 – 16.37)	15.28 (14.62 – 15.90)	13.59 (12.63 – 14.41)	13.48 (12.59 – 14.31)	13.11 (12.31 – 13.85)	12.86 (11.99 – 13.63)	12.51 (11.45 – 13.47)	12.20 (11.18 – 13.13)	12.01 (10.83 – 13.07)	11.74 (10.56 – 12.83)	11.00 (8.16 – 13.64)	9.43 (8.77 – 10.06)	9.17 (6.99 – 11.33)	6.74 (5.20 – 8.31)	6.67 (5.36 – 8.11)	5.82 (4.74 – 6.91)	Placebo

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR >1 favours treatment in a given column.

Figure 22: League table summary of relative risks for the PASI 75 response at the end of induction analyses; baseline risk and duration of psoriasis-adjusted; restricted evidence network

Ixekizumab 80 mg Q2W													
1.02 (0.97 – 1.07)	**Guselkumab 100 mg**												
1.08 (1.00 – 1.16)	1.06 (0.97 – 1.15)	**Infliximab 5 mg/kg**											
1.08 (1.03 – 1.14)	1.07 (1.01 – 1.13)	1.01 (0.93 – 1.09)	**Secukinumab 300 mg**										
1.22 (1.14 – 1.32)	1.20 (1.12 – 1.32)	1.14 (1.04 – 1.25)	1.13 (1.05 – 1.23)	**Ustekinumab 90 mg**									
1.23 (1.15 – 1.33)	1.21 (1.11 – 1.32)	1.14 (1.04 – 1.25)	1.13 (1.07 – 1.21)	1.00 (0.91 – 1.10)	**Secukinumab 150 mg**								
1.27 (1.18 – 1.36)	1.25 (1.17 – 1.33)	1.18 (1.06 – 1.31)	1.17 (1.08 – 1.27)	1.04 (0.93 – 1.14)	1.03 (0.93 – 1.14)	**Adalimumab 40 mg**							
1.29 (1.21 – 1.39)	1.27 (1.18 – 1.38)	1.20 (1.10 – 1.32)	1.19 (1.11 – 1.29)	1.06 (0.98 – 1.13)	1.05 (0.96 – 1.15)	1.02 (0.93 – 1.12)	**Ustekinumab 45 mg**						
1.33 (1.23 – 1.45)	1.31 (1.20 – 1.45)	1.23 (1.11 – 1.39)	1.22 (1.13 – 1.35)	1.09 (0.97 – 1.21)	1.08 (0.97 – 1.20)	1.05 (0.95 – 1.17)	1.03 (0.93 – 1.15)	**Ustekinumab 45/90 mg**					
1.76 (1.64 – 1.89)	1.73 (1.59 – 1.88)	1.63 (1.49 – 1.79)	1.62 (1.50 – 1.75)	1.44 (1.31 – 1.56)	1.43 (1.31 – 1.56)	1.39 (1.25 – 1.53)	1.36 (1.24 – 1.48)	1.32 (1.19 – 1.47)	**Etanercept 50 mg BIW**				
1.80 (1.44 – 2.41)	1.77 (1.41 – 2.39)	1.67 (1.32 – 2.25)	1.66 (1.32 – 2.22)	1.47 (1.16 – 1.98)	1.46 (1.16 – 1.97)	1.42 (1.12 – 1.93)	1.39 (1.10 – 1.87)	1.35 (1.06 – 1.83)	1.02 (0.82 – 1.36)	**Erelzi 50 mg**			
2.44 (1.96 – 3.17)	2.40 (1.93 – 3.12)	2.27 (1.80 – 3.00)	2.25 (1.80 – 2.93)	1.99 (1.58 – 2.61)	1.99 (1.58 – 2.60)	1.93 (1.54 – 2.50)	1.89 (1.51 – 2.46)	1.84 (1.46 – 2.40)	1.39 (1.12 – 1.80)	1.36 (0.95 – 1.91)	**Etanercept 50 mg QW**		
2.48 (2.03 – 3.13)	2.45 (1.99 – 3.10)	2.31 (1.87 – 2.92)	2.29 (1.86 – 2.89)	2.03 (1.64 – 2.56)	2.02 (1.64 – 2.56)	1.96 (1.58 – 2.51)	1.92 (1.56 – 2.43)	1.87 (1.50 – 2.38)	1.41 (1.16 – 1.77)	1.38 (0.98 – 1.90)	1.02 (0.74 – 1.39)	**Etanercept 25 mg BIW**	
16.38 (15.86 – 16.81)	16.14 (15.44 – 16.72)	15.22 (14.19 – 16.24)	15.11 (14.40 – 15.74)	13.39 (12.37 – 14.25)	13.33 (12.37 – 14.23)	12.94 (12.07 – 13.73)	12.68 (11.79 – 13.48)	12.33 (11.23 – 13.35)	9.32 (8.65 – 10.02)	9.12 (6.78 – 11.41)	6.71 (5.16 – 8.35)	6.59 (5.22 – 8.09)	**Placebo**

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR >1 favours treatment in a given column.

i) Please produce a safety NMA for the decision comparator set (restricted network), like in Figures 21–23 of Appendix D. Please provide unadjusted results and results adjusted for baseline risk.

A safety NMA for the restricted network has been conducted as requested. Unadjusted and baseline-risk adjusted analyses are provided in Figure 23 to Figure 28. Similar to findings reported from other NMAs, guselkumab demonstrates comparable safety compared with alternative biologics at the end of induction.

Model fit statistics are summarised in Table 11.

Table 11: Model fit statistics; safety NMAs

	AE	SAE	WDAE
Unadjusted – Restricted Network	Beta: NA SD: 0.04 (0.0003 to 0.13) DIC: 589.61 Resdev: 80.66 vs. 85 data points	Beta: NA SD: 0.16 (0.01 to 0.50) DIC: 389.17 Resdev: 78.05 vs. 87 data points	Beta: NA SD: 0.12 (0.01 to 0.41) DIC: 394.48 Resdev: 74.92 vs. 92 data points
Baseline risk Adjusted NMA – Restricted Network	Beta: -0.22 (-0.40 to 0.02) SD: 0.04 (0.0009 to 0.12) DIC: 594.87 Resdev: 84.42 vs. 85 data points	Beta: -0.86 (-1.11 to -0.58) SD: 0.10 (0.01 to 0.34) DIC: 392.61 Resdev: 82.80 vs. 87 data points	Beta: -0.58 (-0.82 to -0.29) SD: 0.11 (0.003 to 0.37) DIC: 404.19 Resdev: 82.23 vs. 92 data points

Key: AE, adverse event; DIC, deviance information criteria; NMA, network meta-analysis; Resdev, residual deviance; SAE, serious adverse event; SD, standard deviation; WDAE, withdrawal due to adverse event.

Figure 23: League table summary of relative risks for the AE rate at the end of induction analyses; unadjusted; restricted evidence network

Placebo											
0.98 (0.90 – 1.07)	Ustekinumab 90 mg										
1.01 (0.83 – 1.26)	1.03 (0.84 – 1.28)	Etanercept 50 mg QW									
0.93 (0.84 – 1.03)	0.94 (0.84 – 1.08)	0.92 (0.73 – 1.14)	Guselkumab 100 mg								
0.93 (0.86 – 1.00)	0.94 (0.86 – 1.02)	0.92 (0.73 – 1.12)	1.00 (0.88 – 1.13)	Ustekinumab 45 mg							
0.91 (0.85 – 0.99)	0.93 (0.84 – 1.04)	0.91 (0.72 – 1.11)	0.98 (0.89 – 1.08)	0.98 (0.89 – 1.10)	Adalimumab 40 mg						
0.90 (0.83 – 0.98)	0.92 (0.81 – 1.03)	0.89 (0.70 – 1.11)	0.97 (0.84 – 1.10)	0.97 (0.87 – 1.09)	0.99 (0.88 – 1.09)	Ustekinumab 45/90 mg					
0.89 (0.84 – 0.95)	0.91 (0.82 – 1.00)	0.89 (0.71 – 1.06)	0.96 (0.85 – 1.08)	0.96 (0.88 – 1.06)	0.97 (0.89 – 1.07)	0.99 (0.89 – 1.09)	Etanercept 50 mg BIW				
0.86 (0.80 – 0.92)	0.88 (0.78 – 0.97)	0.85 (0.68 – 1.03)	0.93 (0.81 – 1.04)	0.93 (0.84 – 1.03)	0.94 (0.85 – 1.04)	0.95 (0.87 – 1.05)	0.96 (0.88 – 1.05)	Secukinumab 300 mg			
0.84 (0.79 – 0.90)	0.85 (0.77 – 0.95)	0.83 (0.67 – 1.01)	0.90 (0.79 – 1.02)	0.91 (0.82 – 1.00)	0.92 (0.83 – 1.01)	0.93 (0.84 – 1.03)	0.94 (0.87 – 1.01)	0.98 (0.89 – 1.08)	Ixekizumab 80 mg Q2W		
0.83 (0.78 – 0.90)	0.85 (0.76 – 0.95)	0.83 (0.66 – 1.00)	0.90 (0.79 – 1.01)	0.90 (0.82 – 1.01)	0.92 (0.82 – 1.02)	0.93 (0.83 – 1.03)	0.94 (0.86 – 1.03)	0.97 (0.91 – 1.04)	1.00 (0.90 – 1.10)	Secukinumab 150 mg	
0.77 (0.71 – 0.87)	0.79 (0.69 – 0.92)	0.77 (0.61 – 0.96)	0.84 (0.72 – 0.97)	0.84 (0.74 – 0.96)	0.85 (0.75 – 0.97)	0.86 (0.76 – 0.99)	0.87 (0.78 – 0.98)	0.90 (0.81 – 1.04)	0.93 (0.81 – 1.06)	0.93 (0.83 – 1.06)	Infliximab 5 mg/kg

Key: AE, adverse event; BIW, biweekly; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR <1 favours treatment in a given column.

Figure 24: League table summary of relative risks for the AE rate at the end of induction analyses; baseline-risk adjusted; restricted evidence network

Placebo											
0.98 (0.90 – 1.07)	Ustekinumab 90 mg										
1.00 (0.84 – 1.24)	1.02 (0.84 – 1.27)	Etanercept 50 mg QW									
0.94 (0.86 – 1.04)	0.96 (0.84 – 1.09)	0.94 (0.75 – 1.16)	Guselkumab 100 mg								
0.93 (0.86 – 1.00)	0.94 (0.86 – 1.03)	0.93 (0.75 – 1.12)	0.99 (0.87 – 1.11)	Ustekinumab 45 mg							
0.91 (0.85 – 0.98)	0.93 (0.83 – 1.03)	0.91 (0.73 – 1.10)	0.97 (0.88 – 1.07)	0.98 (0.89 – 1.09)	Adalimumab 40 mg						
0.90 (0.83 – 0.98)	0.91 (0.81 – 1.02)	0.91 (0.72 – 1.08)	0.96 (0.84 – 1.08)	0.97 (0.87 – 1.09)	0.99 (0.89 – 1.10)	Ustekinumab 45/90 mg					
0.90 (0.86 – 0.95)	0.91 (0.83 – 1.00)	0.90 (0.73 – 1.08)	0.95 (0.86 – 1.06)	0.97 (0.89 – 1.05)	0.99 (0.90 – 1.08)	1.00 (0.92 – 1.10)	Etanercept 50 mg BIW				
0.86 (0.80 – 0.92)	0.88 (0.78 – 0.97)	0.86 (0.69 – 1.04)	0.91 (0.81 – 1.02)	0.93 (0.84 – 1.02)	0.94 (0.86 – 1.04)	0.96 (0.87 – 1.05)	0.96 (0.88 – 1.04)	Secukinumab 300 mg			
0.84 (0.78 – 0.91)	0.85 (0.76 – 0.95)	0.84 (0.67 – 1.01)	0.89 (0.79 – 1.00)	0.90 (0.82 – 1.00)	0.92 (0.84 – 1.03)	0.93 (0.81 – 1.03)	0.93 (0.86 – 1.01)	0.98 (0.91 – 1.05)	Secukinumab 150 mg		
0.84 (0.79 – 0.90)	0.85 (0.77 – 0.95)	0.84 (0.67 – 1.02)	0.89 (0.80 – 1.00)	0.91 (0.82 – 0.99)	0.93 (0.84 – 1.01)	0.93 (0.85 – 1.03)	0.93 (0.87 – 1.00)	0.98 (0.89 – 1.07)	1.00 (0.91 – 1.10)	Ixekizumab 80 mg Q2W	
0.76 (0.70 – 0.84)	0.77 (0.68 – 0.89)	0.76 (0.61 – 0.94)	0.81 (0.71 – 0.93)	0.82 (0.73 – 0.93)	0.83 (0.74 – 0.95)	0.84 (0.76 – 0.96)	0.84 (0.77 – 0.96)	0.88 (0.79 – 1.00)	0.91 (0.80 – 1.02)	0.90 (0.82 – 1.03)	Infliximab 5 mg/kg

Key: AE, adverse event; BIW, biweekly; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR <1 favours treatment in a given column.

Figure 25: League table summary of relative risks for the SAE rate at the end of induction analyses; unadjusted; restricted evidence network

Ustekinumab 45 mg											
0.91 (0.44 – 2.07)	**Etanercept 50 mg BIW**										
0.91 (0.35 – 2.36)	0.98 (0.43 – 2.20)	**Ustekinumab 45/90 mg**									
0.92 (0.43 – 1.93)	0.99 (0.45 – 2.07)	0.99 (0.40 – 2.71)	**Ustekinumab 90 mg**								
0.82 (0.34 – 2.14)	0.88 (0.47 – 1.74)	0.90 (0.29 – 2.32)	0.91 (0.36 – 2.34)	**Ixekizumab 80 mg Q2W**							
0.79 (0.39 – 1.50)	0.82 (0.52 – 1.42)	0.85 (0.43 – 1.75)	0.87 (0.40 – 1.68)	0.95 (0.47 – 2.07)	**Placebo**						
0.72 (0.28 – 1.86)	0.77 (0.36 – 1.79)	0.79 (0.33 – 2.20)	0.79 (0.29 – 2.03)	0.89 (0.37 – 2.15)	0.93 (0.53 – 1.73)	**Adalimumab 40 mg**					
0.72 (0.28 – 1.86)	0.77 (0.35 – 1.74)	0.79 (0.34 – 1.90)	0.80 (0.31 – 2.02)	0.87 (0.33 – 2.38)	0.92 (0.48 – 1.86)	0.97 (0.41 – 2.46)	**Secukinumab 150 mg**				
0.72 (0.28 – 1.79)	0.77 (0.35 – 1.69)	0.78 (0.37 – 1.68)	0.79 (0.31 – 1.94)	0.86 (0.37 – 2.24)	0.93 (0.47 – 1.79)	0.99 (0.38 – 2.43)	1.00 (0.52 – 1.76)	**Secukinumab 300 mg**			
0.66 (0.20 – 2.37)	0.72 (0.25 – 2.18)	0.75 (0.23 – 2.75)	0.75 (0.23 – 2.66)	0.84 (0.25 – 2.81)	0.86 (0.32 – 2.66)	0.92 (0.29 – 3.49)	0.92 (0.30 – 3.34)	0.94 (0.31 – 3.30)	**Etanercept 50 mg QW**		
0.68 (0.23 – 1.95)	0.74 (0.29 – 1.89)	0.74 (0.26 – 2.19)	0.73 (0.26 – 2.19)	0.82 (0.29 – 2.41)	0.86 (0.40 – 1.88)	0.94 (0.43 – 2.05)	0.94 (0.34 – 2.63)	0.95 (0.34 – 2.73)	1.00 (0.25 – 3.50)	**Guselkumab 100 mg**	
0.52 (0.20 – 1.50)	0.55 (0.22 – 1.40)	0.57 (0.21 – 1.73)	0.57 (0.20 – 1.69)	0.65 (0.24 – 1.73)	0.68 (0.30 – 1.48)	0.71 (0.25 – 1.96)	0.73 (0.26 – 2.09)	0.72 (0.28 – 2.04)	0.78 (0.21 – 2.76)	0.77 (0.24 – 2.45)	**Infliximab 5 mg/kg**

Key: BIW, biweekly; RR, relative risk; SAE, serious adverse event; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR <1 favours treatment in a given column.

Figure 26: League table summary of relative risks for the SAE rate at the end of induction analyses; baseline-risk adjusted; restricted evidence network

Ustekinumab 45 mg											
0.96 (0.44 – 2.08)	Ustekinumab 45/90 mg										
0.87 (0.42 – 1.81)	0.90 (0.40 – 2.03)	Ustekinumab 90 mg									
0.83 (0.43 – 1.51)	0.87 (0.44 – 1.64)	0.94 (0.51 – 1.84)	Etanercept 50 mg BIW								
0.84 (0.39 – 1.69)	0.86 (0.44 – 1.78)	0.95 (0.47 – 1.90)	1.00 (0.59 – 1.74)	Ixekizumab 80 mg Q2W							
0.77 (0.42 – 1.25)	0.79 (0.44 – 1.38)	0.88 (0.48 – 1.49)	0.91 (0.65 – 1.23)	0.91 (0.56 – 1.40)	Placebo						
0.72 (0.37 – 1.33)	0.75 (0.38 – 1.43)	0.84 (0.43 – 1.54)	0.87 (0.53 – 1.41)	0.87 (0.47 – 1.52)	0.94 (0.66 – 1.40)	Adalimumab 40 mg					
0.72 (0.34 – 1.43)	0.74 (0.39 – 1.33)	0.81 (0.39 – 1.73)	0.85 (0.48 – 1.50)	0.84 (0.43 – 1.58)	0.93 (0.60 – 1.51)	0.98 (0.54 – 1.80)	Secukinumab 300 mg				
0.69 (0.33 – 1.46)	0.71 (0.33 – 1.53)	0.79 (0.36 – 1.69)	0.82 (0.45 – 1.55)	0.82 (0.40 – 1.66)	0.91 (0.53 – 1.60)	0.95 (0.53 – 1.84)	0.97 (0.49 – 2.00)	Guselkumab 100 mg			
0.68 (0.33 – 1.40)	0.70 (0.32 – 1.46)	0.78 (0.37 – 1.65)	0.80 (0.45 – 1.47)	0.82 (0.40 – 1.59)	0.90 (0.56 – 1.51)	0.95 (0.48 – 1.77)	0.94 (0.55 – 1.73)	0.98 (0.46 – 2.03)	Secukinumab 150 mg		
0.50 (0.21 – 1.34)	0.53 (0.20 – 1.42)	0.59 (0.22 – 1.54)	0.61 (0.27 – 1.37)	0.61 (0.24 – 1.54)	0.66 (0.31 – 1.52)	0.70 (0.30 – 1.76)	0.72 (0.29 – 1.84)	0.74 (0.29 – 1.95)	0.75 (0.31 – 1.91)	Etanercept 50 mg QW	
0.37 (0.18 – 0.72)	0.38 (0.19 – 0.76)	0.42 (0.21 – 0.86)	0.44 (0.26 – 0.75)	0.44 (0.23 – 0.82)	0.49 (0.32 – 0.76)	0.51 (0.28 – 0.92)	0.52 (0.29 – 1.01)	0.54 (0.27 – 1.14)	0.54 (0.29 – 1.07)	0.72 (0.29 – 1.71)	Infliximab 5 mg/kg

Key: BIW, biweekly; RR, relative risk; SAE, serious adverse event; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR <1 favours treatment in a given column.

Figure 27: League table summary of relative risks for the WDAE rate at the end of induction analyses; unadjusted; restricted evidence network

Ustekinumab 45 mg													
0.53 (0.15 – 1.66)	**Etanercept 50 mg QW**												
0.46 (0.16 – 1.22)	0.86 (0.27 – 2.60)	**Secukinumab 150 mg**											
0.43 (0.18 – 0.97)	0.81 (0.26 – 2.74)	0.94 (0.38 – 2.84)	**Ustekinumab 90 mg**										
0.38 (0.14 – 1.11)	0.73 (0.23 – 2.34)	0.86 (0.43 – 1.74)	0.89 (0.36 – 2.27)	**Secukinumab 300 mg**									
0.32 (0.14 – 0.66)	0.60 (0.24 – 1.62)	0.71 (0.35 – 1.46)	0.76 (0.35 – 1.43)	0.84 (0.41 – 1.68)	**Placebo**								
0.32 (0.12 – 0.82)	0.60 (0.20 – 1.92)	0.72 (0.28 – 1.82)	0.76 (0.27 – 1.80)	0.85 (0.34 – 2.07)	1.00 (0.55 – 1.74)	**Adalimumab 40 mg**							
0.28 (0.07 – 1.09)	0.56 (0.13 – 2.20)	0.62 (0.20 – 2.10)	0.66 (0.15 – 2.57)	0.73 (0.22 – 2.41)	0.88 (0.30 – 2.75)	0.88 (0.26 – 3.25)	**Ustekinumab 45/90 mg**						
0.26 (0.09 – 0.81)	0.49 (0.14 – 1.83)	0.58 (0.19 – 1.84)	0.60 (0.21 – 1.75)	0.68 (0.23 – 2.11)	0.80 (0.35 – 1.93)	0.82 (0.36 – 1.85)	0.93 (0.21 – 3.72)	**Guselkumab 100 mg**					
0.27 (0.11 – 0.61)	0.50 (0.19 – 1.37)	0.60 (0.25 – 1.33)	0.62 (0.28 – 1.25)	0.69 (0.32 – 1.53)	0.81 (0.50 – 1.36)	0.81 (0.38 – 1.86)	0.93 (0.27 – 2.89)	1.01 (0.37 – 2.81)	**Etanercept 50 mg BIW**				
0.21 (0.04 – 1.25)	0.38 (0.07 – 2.46)	0.45 (0.10 – 2.67)	0.47 (0.10 – 2.83)	0.52 (0.12 – 3.19)	0.62 (0.15 – 3.54)	0.65 (0.13 – 3.39)	0.72 (0.09 – 5.84)	0.78 (0.14 – 5.32)	0.73 (0.19 – 4.80)	**Etanercept 25 mg BIW**			
0.19 (0.03 – 1.39)	0.36 (0.06 – 2.75)	0.42 (0.07 – 3.02)	0.44 (0.08 – 2.93)	0.48 (0.09 – 3.61)	0.58 (0.11 – 4.06)	0.59 (0.10 – 4.79)	0.66 (0.09 – 6.16)	0.69 (0.11 – 6.51)	0.71 (0.15 – 3.84)	0.95 (0.09 – 9.23)	**Erelzi 50 mg**		
0.19 (0.06 – 0.51)	0.36 (0.12 – 1.16)	0.42 (0.17 – 1.13)	0.44 (0.17 – 1.12)	0.50 (0.19 – 1.31)	0.60 (0.30 – 1.14)	0.61 (0.24 – 1.41)	0.66 (0.18 – 2.39)	0.74 (0.24 – 2.18)	0.72 (0.34 – 1.55)	0.93 (0.17 – 4.57)	1.01 (0.14 – 5.83)	**Infliximab 5 mg/kg**	
0.16 (0.05 – 0.45)	0.31 (0.11 – 0.93)	0.37 (0.15 – 0.89)	0.39 (0.14 – 0.87)	0.43 (0.17 – 1.00)	0.51 (0.26 – 0.96)	0.51 (0.22 – 1.19)	0.56 (0.18 – 1.79)	0.63 (0.21 – 1.79)	0.62 (0.31 – 1.17)	0.81 (0.13 – 3.87)	0.84 (0.14 – 4.76)	0.86 (0.31 – 2.13)	**Ixekizumab 80 mg Q2W**

Key: BIW, biweekly; RR, relative risk; Q2W, every two weeks; QW, once weekly; WDAE, withdrawal due to adverse event.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR <1 favours treatment in a given column.

Figure 28: League table summary of relative risks for the WDAE rate at the end of induction analyses; baseline-risk adjusted; restricted evidence network

Ustekinumab 45 mg													
0.59 (0.22 – 1.57)	**Secukinumab 150 mg**												
0.54 (0.20 – 1.31)	0.90 (0.44 – 1.80)	**Secukinumab 300 mg**											
0.53 (0.16 – 1.68)	0.90 (0.29 – 2.69)	1.03 (0.37 – 2.64)	**Ustekinumab 45/90 mg**										
0.45 (0.20 – 1.07)	0.76 (0.33 – 1.98)	0.87 (0.37 – 2.06)	0.85 (0.29 – 2.71)	**Ustekinumab 90 mg**									
0.45 (0.15 – 1.48)	0.77 (0.19 – 2.55)	0.87 (0.15 – 2.96)	0.87 (0.13 – 3.59)	0.98 (0.36 – 3.17)	**Etanercept 50 mg QW**								
0.40 (0.19 – 0.78)	0.66 (0.34 – 1.32)	0.75 (0.40 – 1.43)	0.75 (0.30 – 1.87)	0.89 (0.48 – 1.48)	0.88 (0.30 – 2.79)	**Placebo**							
0.37 (0.16 – 0.89)	0.62 (0.29 – 1.42)	0.72 (0.32 – 1.57)	0.71 (0.26 – 2.00)	0.83 (0.40 – 1.67)	0.84 (0.27 – 2.33)	0.94 (0.60 – 1.53)	**Adalimumab 40 mg**						
0.36 (0.13 – 1.01)	0.61 (0.23 – 1.70)	0.70 (0.25 – 1.81)	0.69 (0.22 – 2.27)	0.79 (0.31 – 2.01)	0.83 (0.21 – 2.54)	0.91 (0.43 – 1.97)	0.96 (0.43 – 2.22)	**Guselkumab 100 mg**					
0.32 (0.08 – 1.71)	0.56 (0.14 – 3.02)	0.64 (0.16 – 3.23)	0.64 (0.13 – 3.63)	0.72 (0.19 – 3.58)	0.75 (0.15 – 4.52)	0.83 (0.24 – 3.81)	0.88 (0.23 – 4.42)	0.90 (0.21 – 5.11)	**Etanercept 25 mg BIW**				
0.32 (0.15 – 0.68)	0.54 (0.26 – 1.15)	0.61 (0.30 – 1.24)	0.61 (0.23 – 1.55)	0.72 (0.38 – 1.29)	0.72 (0.25 – 2.20)	0.81 (0.57 – 1.13)	0.87 (0.48 – 1.52)	0.89 (0.38 – 2.01)	0.98 (0.22 – 3.26)	**Etanercept 50 mg BIW**			
0.23 (0.03 – 1.20)	0.40 (0.06 – 2.08)	0.45 (0.08 – 2.06)	0.44 (0.06 – 2.74)	0.51 (0.08 – 2.34)	0.53 (0.07 – 2.78)	0.60 (0.10 – 2.55)	0.63 (0.11 – 2.77)	0.63 (0.11 – 3.29)	0.67 (0.07 – 4.34)	0.73 (0.14 – 3.07)	**Erelzi 50 mg**		
0.24 (0.10 – 0.56)	0.41 (0.18 – 0.93)	0.46 (0.21 – 1.00)	0.46 (0.17 – 1.22)	0.54 (0.25 – 1.11)	0.54 (0.17 – 2.07)	0.62 (0.37 – 1.04)	0.66 (0.32 – 1.30)	0.69 (0.27 – 1.56)	0.73 (0.15 – 2.68)	0.76 (0.43 – 1.31)	1.05 (0.22 – 5.94)	**Ixekizumab 80 mg Q2W**	
0.15 (0.07 – 0.33)	0.25 (0.12 – 0.59)	0.28 (0.12 – 0.64)	0.28 (0.10 – 0.87)	0.33 (0.16 – 0.67)	0.34 (0.11 – 0.85)	0.37 (0.25 – 0.64)	0.39 (0.21 – 0.81)	0.41 (0.17 – 1.08)	0.45 (0.09 – 1.86)	0.46 (0.27 – 0.86)	0.64 (0.14 – 3.85)	0.60 (0.31 – 1.35)	**Infliximab 5 mg/kg**

Key: BIW, biweekly; RR, relative risk; Q2W, every two weeks; QW, once weekly; WDAE, withdrawal due to adverse event.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR <1 favours treatment in a given column.

j) How were the covariates included in the models: as mean-centred or centred otherwise? Please clarify whether the meta-regression models were parametrised as having a common effect against all treatment-placebo comparisons, or had an exchangeable or unrelated effect.

A given covariate was included in each model as a mean-centred covariate. The meta-regressions were parametrised as having a common effect against all treatment-placebo comparisons.

A8. **PRIORITY QUESTION**: Please reproduce Table 19 in Document B of the company submission including the ustekinumab arms of the trial and the 95% confidence intervals. → Clarification call: the question should state adalimumab instead of ustekinumab.

It is not feasible to reproduce this table including the adalimumab arm given that patients crossed-over at week 52. In absence of this, Tables 15 – 19 of Document B include a detailed breakdown of adverse events including adalimumab arm.

A9. **PRIORITY QUESTION**: Please outline the arithmetic used to derive the following outcomes for placebo, guselkumab, ustekinumab and adalimumab from the central estimates in Table 14 of Document B: PASI75, PASI90, PASI100, DLQI 0/1 and SAEs. This can be supplied in an excel spreadsheet.

The values reported in Table 14 of Document B are relative risks. The WinBUGS code to derive effect estimates are largely based on code reported in the NICE TSD Evidence Synthesis series. This code was previously provided in Table 10 of Appendix D.

A10. Blinding in the VOYAGE and NAVIGATE trials appears to be achieved by giving placebo injections during gaps between dosing times for the adalimumab, guselkumab and ustekinumab regimens. Were similar methods used in other head-to-head and placebo-controlled trials of anti-IL and anti-TNF agents?

A summary of methods of treatment blinding used in other head-to-head and placebo-controlled trials of anti-IL and anti-TNF agents is provided in Table 12.

With the exception of the ACCEPT trial, which was not blinded between active treatments, all studies were double-blind in nature and involved dummy placebo injections matching the schedule of the active comparator or comparators.

Table 12: Summary of methods of treatment blinding

Trial	NCT #	Comparators	Blinding
CHAMPION	NCT00235820	Adalimumab Placebo Methotrexate	Adalimumab (Humira; Abbott Laboratories) or matching placebo for SC injection was provided as sterile preservative-free solution in prefilled syringes. Oral methotrexate tablets were supplied by Wyeth Pharma (Munster, Germany), and placebo tablets were supplied by Abbott GmbH & Co. KG (Ludwigshafen, Germany).
REVEAL	NCT00237887	Adalimumab Placebo	SC injections of: (1) an initial dose of adalimumab (80 mg) at week 0 followed by adalimumab (40 mg) eow beginning at week 1 and through week 15; or (2) placebo injections at week 0 and placebo eow beginning at week 1 and through week 15. Adalimumab- and placebo-filled syringes were identically labelled and packaged, and self-administered by patients.
Asahina 2010	NCT00338754	Adalimumab Placebo	Patients were randomised 1:1:1:1 to one of four treatment regimens: (i) adalimumab 40 mg eow; (ii) adalimumab 40 mg eow starting at week 2 with a loading dose of adalimumab 80 mg at week 0; (iii) adalimumab 80 mg eow; or (iv) placebo eow. Adalimumab 40 mg/0.8 mL and placebo 0.8 mL were supplied in two-vial cartons (adalimumab + adalimumab, adalimumab + placebo, or placebo + placebo). The study drug was given as two SC injections starting at week 0 for 24 weeks.
Cai 2017	NCT01646073	Adalimumab Placebo	Patients in Period A were randomized 4:1 to receive adalimumab 40 mg every-other-week (following a single 80 mg dose), or matching placebo.
ACCEPT	NCT00454584	Ustekinumab Etanercept	Patients were aware of their treatment assignment, although patients who were randomly assigned to ustekinumab received double injections (one injection of active treatment and one injection of placebo) to maintain blinding for the dose.
PHOENIX 1	NCT00267969	Ustekinumab Placebo	Patients received placebo injections as needed to preserve the blind.
PHOENIX 2	NCT00307437	Ustekinumab Placebo	At baseline, patients were randomised 1:1:1 to receive ustekinumab 45 mg or 90 mg by subcutaneous injection at weeks 0, 4, and every 12 weeks, or placebo at weeks 0 and 4.
Igarashi 2012	NCT00723528	Ustekinumab Placebo	Patients were randomized (2:2:1) to receive ustekinumab 45 or 90 mg by SC injection at weeks 0, 4, and every 12 weeks, or placebo at weeks 0 and 4.

PEARL	NCT00747344	Ustekinumab Placebo	Patients were randomized (1:1) to SC injections in one of two treatment regimens: (1) ustekinumab 45 mg at weeks 0, 4 and 16 and an injection of placebo at week 12 to maintain the study blind or (2) placebo at weeks 0 and 4, followed by crossover to ustekinumab 45 mg at weeks 12 and 16.
LOTUS	NCT00096980	Ustekinumab Placebo	Patients randomised 1:1 to receive SC injections of ustekinumab 45 mg or placebo at weeks 0 and 4. At week 12, patients randomised to placebo crossed over to receive ustekinumab 45 mg, and patients randomised to ustekinumab received placebo to maintain the blind.
FEATURE	NCT01555125	Secukinumab Placebo	Both placebo and the active drug were dosed once weekly using the pre-filled syringe at baseline and at weeks 1, 2 and 3, then every 4 weeks starting from week 4. The pre-filled syringe included an automatically retracting needle designed to avoid accidental needle injuries; each unit contained 150 mg secukinumab in 1 mL of solution or matching placebo. Subjects in the secukinumab 300-mg arm received two 150-mg SC injections and those in the 150-mg arm received one 150-mg SC injection and one placebo SC injection to maintain blinding.
CLEAR	NCT02074982	Secukinumab Ustekinumab	Secukinumab was administered at baseline and weeks 1, 2, and 3, then every 4 weeks from week 4 to week 48; ustekinumab at baseline and week 4, then every 12 weeks from week 16 to week 40. To maintain blinding, placebo injections matching the secukinumab regimen were given to subjects in the ustekinumab group.
JUNCTURE	NCT01636687	Secukinumab Placebo	During the induction period, subjects in the secukinumab 300 mg group were administered two 150 mg autoinjections, subjects in the secukinumab 150 mg group were administered one 150 mg autoinjection and one placebo autoinjection, and subjects in the placebo group were administered two placebo autoinjections once weekly at Baseline, at Weeks 1, 2 and 3, and then every 4 weeks starting from Week 4.
ERASURE	NCT01365455	Secukinumab Placebo	Patients randomly assigned to secukinumab in either study received either two 150-mg SC secukinumab injections (i.e., 300 mg total) or one 150-mg injection plus one placebo injection, with both injections administered once weekly at baseline and at weeks 1, 2, 3, and 4 and then every 4 weeks until week 48. Patients randomly assigned to etanercept received 50 mg administered subcutaneously twice weekly from baseline until week 12 and then once weekly through week 51, in accordance with the standard dosing regimen. In the FIXTURE study, the placebo group received placebo injections corresponding to the secukinumab and the etanercept regimens, and the secukinumab and etanercept groups received placebo injections corresponding to the other active-drug regimen, in
FIXTURE	NCT01358578	Secukinumab Etanercept Placebo	

			order to maintain a double-dummy design. In the ERASURE study, patients randomly assigned to placebo received placebo injections corresponding to the secukinumab regimens.
SCULPTURE	NCT01406938	Secukinumab	Eligible patients were randomised (1:1) to secukinumab at 300 mg or 150 mg, administered via two 150-mg SC injections or one 150-mg subcutaneous and one placebo subcutaneous injection, respectively.
UNCOVER 1	NCT01474512	Ixekizumab Placebo	Patients to receive SC injections of placebo (placebo group), 80 mg of ixekizumab every 2 weeks after a starting dose of 160 mg at week 0 (2-wk dosing group), or 80 mg of ixekizumab every 4 weeks after a starting dose of 160 mg at week 0 (4-wk dosing group). For all trials and trial periods, placebo was given to match all active treatment dosing regimens.
UNCOVER 2 **UNCOVER 3**	NCT01597245 NCT01646177	Ixekizumab Etanercept Placebo	Patients received either ixekizumab 160 mg starting dose followed by 80 mg every 2 weeks or every 4 weeks, etanercept 50 mg twice weekly, or placebo. All patients received two SC injections at week 0 (ixekizumab or placebo for ixekizumab), twice weekly SC injections from weeks 0–11 (etanercept or placebo for etanercept), and one SC injection (ixekizumab or placebo for ixekizumab) at weeks 2, 4, 6, 8, and 10.
IXORA-S	NCT02561806	Ixekizumab Ustekinumab	During the induction period (weeks 0–12), patients randomized to ixekizumab received two SC injections of ixekizumab 80 mg (160 mg total) at week 0, followed by one SC injection of ixekizumab 80 mg every 2 weeks through week 12, and 80 mg every 4 weeks thereafter (Fig. 1). Patients randomised to ustekinumab were dosed at weeks 0, 4, 16, 28 and 40, in accordance with the label, with patients weighing ≤100.0 kg receiving 45 mg SC injections and patients weighing >100.0 kg receiving 90 mg SC injections. To maintain the blinding, patients randomised to ixekizumab received placebo injections matching the ustekinumab dose regimen, and patients in the ustekinumab group received dummy injections of ixekizumab.
Key: eow, every other week; SC, subcutaneous.			

A11. Suicide and suicide ideation appear to be concerns with anti-IL agent treatment. In the trials of guselkumab, patients receiving lithium were excluded. Might this result in an underestimation of the suicide risk?

Patients receiving lithium were excluded on the basis that lithium is associated with psoriasis aggravation or occurrence of psoriasis.[3, 4] Lithium use was also an exclusion criterion in ustekinumab trials (PHOENIX 1, PHOENIX 2 and ACCEPT), but a publication review of trials identified in the SLR could not confirm whether such an exclusion criterion has also been adopted in trials of alternative biologic therapies (that is, full exclusion criteria are not reported in the publications). Consultation with a UK dermatologist confirms that lithium would not be prescribed to patients with plaque psoriasis in clinical practice due to risk of disease exacerbation.

Lithium is a mood stabiliser most commonly prescribed to treat Bipolar Disorder.[5] The prevalence of Bipolar Disorder in psoriasis patients enrolled in the Psoriasis Longitudinal Assessment and Registry (PSOLAR) database is 1.5%.[6] Applying this prevalence to the enrolled patients across the guselkumab trials results in an estimated 41 patients (2,700 x 1.5%) who may have been additionally enrolled should they not have excluded patients receiving lithium. Of these patients, one in ten may have had concomitant serious depression and even a smaller proportion still would be at risk of suicide.

The total number of patients enrolled across the VOYAGE and NAVIGATE trials who had a reported history of depression was 162, as summarised in Table 13. Based on the evidence summarised above, a further 4 patients may have been included in this patient group across all trials. Inclusion of this small number of patients (who, as noted above, would not be automatically at risk of suicide) would not have substantially altered the numbers of patients at risk of suicide and thus we do not believe that the exclusion of patients receiving lithium resulted in an underestimation of the suicide risk.

Table 13: Number of patients with a diagnosis of depression at randomisation in guselkumab trials

Summary of medical history and current diagnoses: depression; randomised patients.				
	Placebo	Guselkumab	Adalimumab	Ustekinumab
VOYAGE 1	14 (8.0%)	21 (6.4%)	27 (8.1%)	N/A
VOYAGE 2	18 (7.3%)	38 (7.7%)	19 (7.7%)	N/A
NAVIGATE	N/A	7 (5.2%)	N/A	18 (13.5%)
Key: N/A, not applicable.				

A12. In the schematic overview of the NAVIGATE trial (Figure 4 of Document B of the company submission), the active treatment phase begins at week 16 and ends at week 44. However, the results (Table 13 of Document B) present a different timeline (weeks 28 to 40). Please clarify.

The active treatment phase of the NAVIGATE trial did begin at Week 16, as per the schematic overview (Figure 4 of Document B of the company submission).

All endpoints were assessed through Weeks 28 to 40 (as per Table 13 of Document B) to align with the end of the induction period of guselkumab and thus allow sufficient dosage to allow an unbiased comparison.

A13. Please provide data for the proportion of LOCF used in the PASI90 and PASI75 graphs from VOYAGE 1 and its extension.

An explanation about how missing data were handled in all of the guselkumab trials is provided below:

<u>VOYAGE 1 and 2</u>
Patients who discontinued study agent due to lack of efficacy or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis, were considered treatment failures.

After the treatment failures were applied, the remaining missing data were handled as follows for all of the efficacy analyses (except for Psoriasis Symptoms and Signs Diary [PSSD]) including the analyses at key visits (Week 16, Week 24, and Week 48) and over time summaries:

- Nonresponder imputation was applied for binary endpoints.
- Last observation carried forward (LOCF) was applied for continuous variables.

In contrast to other efficacy measurements, which were collected every 4 weeks or at longer intervals at study sites, PSSD data were collected daily at home. Therefore, for the analyses related to PSSD, after weekly data were derived and the treatment-failure rules were applied, LOCF was applied for both binary and continuous endpoints for missing PSSD data due to more frequent PSSD data collection.

<u>NAVIGATE</u>
Patients who discontinued study agent due to lack of efficacy or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis were considered treatment failures.

Patients who were randomised (at Week 16), were considered treatment failures starting from the first timepoint after randomisation at which they triggered a treatment failure rule. That is, non-responder patients who were randomised who had triggered a treatment failure rule prior to Week 16 (during the open-label ustekinumab period) were considered non-treatment failures at the time of randomisation.

After the treatment failures were applied, the remaining missing data after Week 16 for randomised patients were handled as follows for all efficacy analyses including the analyses at Week 28 and over time summaries:

- Non-responder imputation rules were applied for binary endpoints
- LOCF rules were applied for continuous endpoints.

After the treatment failure rules were applied, the remaining missing data for all enrolled and treated subjects from Week 0 through Week 16 and nonrandomised patients from Week 16 through Week 40 were not imputed.

VOYAGE 1 extension

Pre-specified analysis:

- **Treatment failure rules (TFR):** the process of marking data for a patient who meets treatment failure criteria (loss of efficacy, worsening of psoriasis, or start of a protocol-prohibited medication) as non-response from the date of treatment failure through the end of the trial (whether or not the patient discontinues)
    - Note: because treatment failures almost always discontinue the trial, using TFR in addition to NRI does not usually change the analysis. It would only matter if a patient met treatment failure criteria, but stayed in the trial.

Sensitivity analysis:

- **Non-responder imputation (NRI):** the process of marking missing data as non-response, without regard to the reason for missing data
- **As observed (AO)**: an analysis in which missing data remains missing → Reported in NICE submission as it was published

A comparative plot showing the PASI 90 response analyses demonstrates good consistency across the different approaches to data handling, as presented in [redacted].

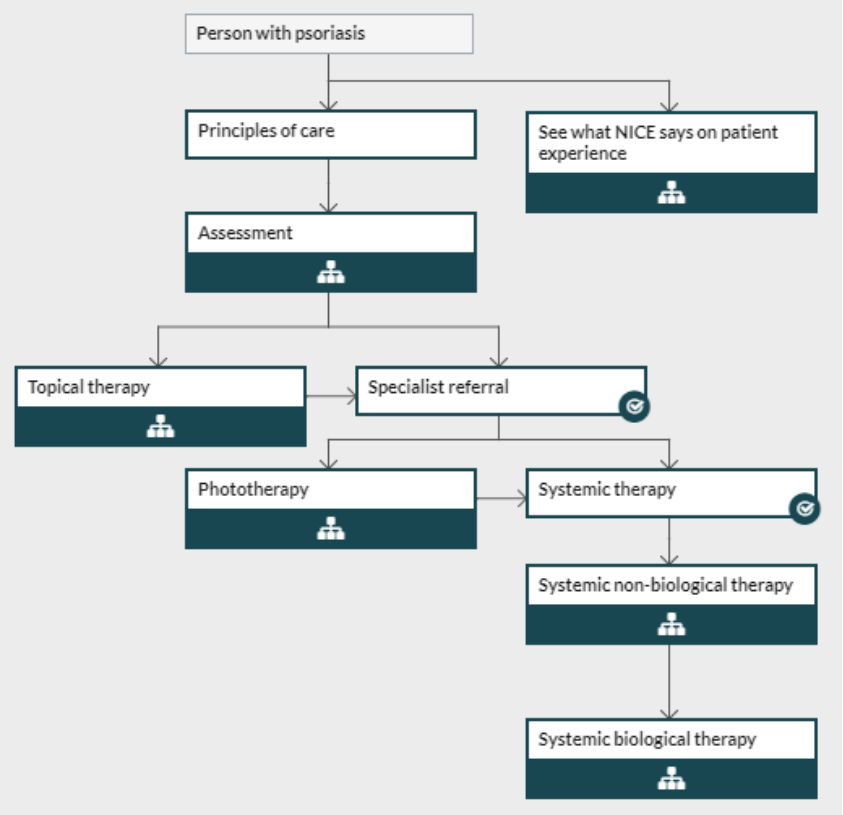
[redacted]

A14. The text in Document B of the company submission states that “Apremilast and DMF are small molecule, non-biologic, oral treatments with significantly lower degrees of efficacy and differing safety profiles to the biologic therapies and would only be considered for use in patients unsuitable for biologic treatment or unwilling to receive

biologic treatment". Figure 1 of Document B of the company submission suggests that patients would only use apremilast or DMF before biologics. Please clarify.

Figure 1 of Document B is aligned with the NICE psoriasis overview that positions non-biologic systemic therapy before biologic systemic therapy, as depicted in Figure 30.

Figure 30: NICE pathway: psoriasis overview



The detailed recommendations for apremilast and DMF are summarised below:

- Apremilast is recommended as an option for treating chronic plaque psoriasis in adults whose disease has not responded to other systemic therapies, including ciclosporin, methotrexate and PUVA, or when these treatments are contraindicated or not tolerated, only if:
    - the disease is severe, as defined by a total PASI of 10 or more and a DLQI of more than 10
    - treatment is stopped if the psoriasis has not responded adequately at 16 weeks; 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 start of treatment

    - the company provides apremilast with the discount agreed in the patient access scheme.

- Dimethyl fumarate (DMF) is recommended as an option for treating plaque psoriasis in adults, only if the disease:

    - is severe, as defined by a total PASI of 10 or more and a DLQI of more than 10 and

    - has not responded to other systemic therapies, including, ciclosporin, methotrexate and PUVA, or these options are contraindicated or not tolerated.

Based on these recommendations, apremilast and DMF were included in the scope as potential comparators to guselkumab. We do not believe this is appropriate as in clinical practice, these treatments would only be considered for use in patients unsuitable for biologic treatment or unwilling to receive biologic treatment. While there is some debate as to whether their use is typically before or after biologic treatment, as summarised in Table 14, there is no debate over the fact that they would not be considered for patients suitable for, and willing to receive biologic treatment; hence why we do not believe apremilast or DMF take up the same position in the treatment pathway as biologic treatments.

Table 14: Summary of comments on the positioning of apremilast and DMF in the treatment pathway: TA419 and TA475

Consultee	Comment
Clinical expert	*"The committee understood from the clinical experts that, in general, apremilast would not displace a biological therapy in the treatment pathway." TA419*
Clinical expert	*"It heard from clinical experts that the positioning of apremilast (either before, or instead of, a biological therapy) would be driven largely by patient choice and intolerance or contraindications to biological therapy such as serious infections." TA419*
NICE Committee	*"The committee agreed that apremilast may not be the preferred treatment at the point in the treatment pathway at which biological therapies are considered (that is, after all systemic treatment have failed), but clinicians would like to have the option to prescribe apremilast at this point." TA419*
Clinical expert	*The committee heard from the clinical expert and the company that the most likely position for dimethyl fumarate is as an alternative to biologicals and apremilast. TA475*
NICE Committee	*The committee agreed that it was appropriate to consider dimethyl fumarate at this position. TA475*

	However, no comparison against biologics was presented, see box below.
NICE Committee	*The committee noted that the company presented 6 pairwise comparisons of different treatment sequences[a]:* • *Dimethyl fumarate before biologicals compared with no dimethyl fumarate **before** biologicals.* • *Dimethyl fumarate compared with apremilast **before** biologicals.* • *Dimethyl fumarate **before** biologicals compared with dimethyl fumarate **after** biologicals. TA475*
Notes: [a], none of these treatment sequences model dimethyl fumarate in the same position as biologics.	

A15. Please provide the equivalent of Figure 13 in Document B of the company submission for:

- PASI100 at the end of induction analysis (2 figures: one with adjusted and one with unadjusted results)
- SAEs (2 figures: adjusted and unadjusted).

Baseline-risk adjusted and unadjusted analyses of PASI 100 on the restricted network are provided in Figure 31 and Figure 32.

Baseline-risk adjusted and unadjusted analyses of SAE rates on the restricted network were previously provided in Figure 25 and Figure 26.

Figure 31: League table summary of relative risks for the PASI 100 response at the end of induction analyses; baseline risk-adjusted; restricted evidence network

Ixekizumab 80 mg Q2W											
1.11 (0.90 – 1.38)	**Guselkumab 100 mg**										
1.36 (1.11 – 1.64)	1.22 (0.96 – 1.51)	**Secukinumab 300 mg**									
1.48 (0.38 – 29.35)	1.32 (0.34 – 26.41)	1.09 (0.28 – 21.87)	**Infliximab 5 mg/kg**								
2.03 (1.65 – 2.53)	1.83 (1.42 – 2.34)	1.50 (1.23 – 1.86)	1.39 (0.07 – 5.51)	**Ustekinumab 45/90 mg**							
2.20 (1.79 – 2.75)	1.97 (1.63 – 2.42)	1.62 (1.31 – 2.05)	1.49 (0.07 – 5.78)	1.08 (0.84 – 1.39)	**Adalimumab 40 mg**						
2.23 (1.71 – 2.92)	2.00 (1.48 – 2.72)	1.64 (1.25 – 2.21)	1.52 (0.08 – 6.08)	1.10 (0.81 – 1.50)	1.02 (0.75 – 1.36)	**Ustekinumab 45 mg**					
2.55 (2.01 – 3.26)	2.28 (1.74 – 3.04)	1.88 (1.55 – 2.34)	1.70 (0.09 – 7.01)	1.25 (0.97 – 1.65)	1.16 (0.88 – 1.53)	1.14 (0.84 – 1.56)	**Secukinumab 150 mg**				
3.33 (2.29 – 4.71)	2.99 (1.99 – 4.34)	2.46 (1.70 – 3.53)	2.25 (0.11 – 9.62)	1.64 (1.10 – 2.39)	1.51 (1.02 – 2.18)	1.49 (1.09 – 2.03)	1.30 (0.88 – 1.90)	**Ustekinumab 90 mg**			
6.57 (5.18 – 8.45)	5.90 (4.42 – 7.96)	4.84 (3.75 – 6.43)	4.45 (0.23 – 17.67)	3.24 (2.43 – 4.36)	2.98 (2.23 – 4.02)	2.96 (2.14 – 4.04)	2.57 (1.92 – 3.53)	1.98 (1.35 – 2.93)	**Etanercept 50 mg BIW**		
11.50 (3.08 – 67.23)	10.30 (2.74 – 60.28)	8.50 (2.26 – 50.06)	7.55 (0.33 – 88.25)	5.65 (1.52 – 33.04)	5.19 (1.39 – 30.39)	5.17 (1.33 – 30.31)	4.52 (1.18 – 26.37)	3.50 (0.89 – 20.22)	1.75 (0.48 – 9.95)	**Etanercept 50 mg QW**	
73.12 (62.90 – 84.10)	65.67 (55.48 – 76.46)	53.86 (46.06 – 63.21)	49.35 (2.48 – 185.30)	35.99 (29.51 – 43.19)	33.27 (28.07 – 38.51)	32.70 (25.31 – 42.66)	28.71 (22.75 – 35.55)	21.93 (15.60 – 31.76)	11.13 (8.61 – 14.07)	6.37 (1.08 – 23.70)	**Placebo**

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR >1 favours treatment in a given column.

Figure 32: League table summary of relative risks for the PASI 100 response at the end of induction analyses; unadjusted; restricted evidence network

Ixekizumab 80 mg Q2W											
1.32 (0.93 – 1.96)	**Secukinumab 300 mg**										
1.60 (0.57 – 4.67)	1.20 (0.41 – 3.55)	**Ustekinumab 45 mg**									
1.70 (0.88 – 3.52)	1.27 (0.60 – 2.83)	1.08 (0.34 – 3.17)	**Guselkumab 100 mg**								
1.73 (0.38 – 29.76)	1.29 (0.29 – 22.13)	1.12 (0.17 – 20.72)	1.02 (0.20 – 19.54)	**Infliximab 5 mg/kg**							
2.15 (1.46 – 3.33)	1.63 (1.12 – 2.41)	1.35 (0.43 – 4.07)	1.29 (0.54 – 2.89)	1.26 (0.07 – 6.30)	**Ustekinumab 45/90 mg**						
2.15 (0.66 – 6.66)	1.61 (0.48 – 5.18)	1.33 (0.93 – 1.97)	1.24 (0.37 – 4.28)	1.18 (0.06 – 8.55)	0.98 (0.29 – 3.36)	**Ustekinumab 90 mg**					
2.38 (1.54 – 4.05)	1.81 (1.41 – 2.47)	1.52 (0.47 – 4.84)	1.44 (0.59 – 3.31)	1.40 (0.08 – 6.85)	1.11 (0.71 – 1.82)	1.13 (0.33 – 4.11)	**Secukinumab 150 mg**				
3.49 (1.66 – 7.42)	2.60 (1.14 – 5.96)	2.24 (0.64 – 6.70)	2.04 (1.43 – 2.91)	1.99 (0.10 – 10.58)	1.59 (0.66 – 3.96)	1.66 (0.45 – 5.64)	1.43 (0.58 – 3.59)	**Adalimumab 40 mg**			
5.99 (3.84 – 9.03)	4.50 (2.74 – 7.25)	3.72 (1.13 – 12.49)	3.57 (1.37 – 7.94)	3.46 (0.21 – 17.19)	2.77 (1.61 – 4.61)	2.78 (0.78 – 10.56)	2.50 (1.40 – 4.07)	1.73 (0.66 – 4.16)	**Etanercept 50 mg BIW**		
10.07 (2.28 – 56.36)	7.53 (1.63 – 41.67)	6.21 (1.05 – 47.00)	5.87 (1.09 – 39.75)	5.59 (0.23 – 67.75)	4.64 (1.05 – 26.04)	4.63 (0.74 – 36.97)	4.21 (0.86 – 22.79)	2.87 (0.52 – 20.75)	1.68 (0.39 – 8.89)	**Etanercept 50 mg QW**	
84.49 (56.14 – 124.50)	62.97 (38.85 – 103.00)	52.79 (19.49 – 129.90)	49.43 (26.09 – 89.57)	47.99 (2.75 – 186.70)	38.49 (22.42 – 70.71)	39.38 (13.26 – 115.10)	34.63 (18.63 – 65.51)	23.94 (12.26 – 48.53)	13.69 (7.45 – 29.02)	8.41 (1.42 – 38.70)	**Placebo**

Key: BIW, biweekly; PASI, Psoriasis Area Severity Index; RR, relative risk; Q2W, every two weeks; QW, once weekly.
Notes: Interventions are ordered from left to right in order of decreasing SUCRA value. For each pairwise comparison, the lower/right-most intervention serves as the reference group. Pairwise comparisons are shown in terms of summary RRs and 95% CrIs. A RR >1 favours treatment in a given column.

A16. Please provide the equivalent of Table 14 and Figures 12, 13, 14 and 16 of Document B for an analysis which does not adjust for covariates.

Unadjusted relative effect analyses are provided in Appendix D in the form of league table summaries. A summary of pairwise comparisons with guselkumab from these unadjusted relative effects analyses (the equivalent of Table 14 of Document B) is provided in Table 15.

The equivalent of Figures 12, 14 and 16 of Document B are Figures 19, 20 and 21 of Appendix D, respectively. The equivalent of Figure 13 of Document B is presented in this response document as Figure 13.

A17. Please provide the full **adverse events** breakdown for **NAVIGATE for weeks 16-32**[2]

The requested breakdown of AE data collected in the active treatment period up to database lock (Week 16 to Week 40) of the NAVIGATE trial is provided in Table 16.

[2] Question sent by e-mail on the 22nd of November as an additional question following A7g

Table 15: Summary of pairwise comparisons with guselkumab from unadjusted relative effects analyses

	Values >1 favour guselkumab 100mg						Values <1 favour guselkumab 100mg		
	PASI 90	**IGA/PGA 0/1**	**PASI 100**	**PASI 75**	**PASI 50**	**DLQI 0/1**	**AE**	**SAE**	**WDAE**
Placebo	35.23 (28.73 – 41.66)	15.73 (14.21 – 16.98)	49.43 (26.09 – 89.57)	15.65 (14.70 – 16.39)	6.31 (6.08 – 6.47)	9.35 (7.60 – 11.06)	1.08 (0.97 – 1.19)	1.16 (0.53 – 2.50)	1.25 (0.52 – 2.86)
Ixekizumab 80mg Q2W	0.79 (0.64 – 0.96)	0.90 (0.81 – 0.99)	0.59 (0.28 – 1.14)	0.94 (0.88 – 1.00)	-	1.00 (0.78 – 1.23)	0.90 (0.79 – 1.02)	1.22 (0.41 – 3.45)	0.63 (0.21 – 1.79)
Secukinumab 300mg	0.93 (0.72 – 1.16)	0.94 (0.84 – 1.04)	0.79 (0.35 – 1.67)	1.02 (0.94 – 1.09)	0.98 (0.93 – 1.03)	1.10 (0.86 – 1.37)	0.93 (0.81 – 1.04)	1.05 (0.37 – 2.94)	1.47 (0.47 – 4.35)
Secukinumab 150mg	1.21 (0.90 – 1.58)	1.12 (0.97 – 1.29)	1.44 (0.59 – 3.31)	1.14 (1.03 – 1.24)	1.02 (0.96 – 1.10)	1.32 (1.02 – 1.68)	0.90 (0.79 – 1.01)	1.06 (0.38 – 2.94)	1.72 (0.54 – 5.26)
Ustekinumab 90mg	1.17 (0.89 – 1.52)	1.14 (1.00 – 1.30)	1.24 (0.37 – 4.28)	1.14 (1.04 – 1.24)	1.01 (0.97 – 1.06)	0.93 (0.73 – 1.19)	1.06 (0.93 – 1.19)	1.37 (0.46 – 3.85)	1.67 (0.57 – 4.76)
Ustekinumab 45/90mg	1.38 (1.02 – 1.83)	1.19 (1.02 – 1.38)	1.29 (0.54 – 2.89)	1.29 (1.15 – 1.45)	-	1.32 (1.02 – 1.70)	0.97 (0.84 – 1.10)	1.35 (0.46 – 3.85)	1.08 (0.27 – 4.76)
Ustekinumab 45mg	1.29 (0.98 – 1.69)	1.24 (1.08 – 1.44)	0.93 (0.32 – 2.94)	1.23 (1.10 – 1.35)	1.05 (0.99 – 1.11)	0.94 (0.74 – 1.19)	1.00 (0.88 – 1.13)	1.47 (0.51 – 4.35)	3.85 (1.23 – 11.11)
Infliximab 5mg/kg	0.83 (0.61 – 1.28)	0.87 (0.78 – 0.97)	1.02 (0.20 – 19.54)	0.93 (0.86 – 1.02)	0.97 (0.93 – 1.02)	-	0.84 (0.72 – 0.97)	0.77 (0.24 – 2.45)	0.74 (0.24 – 2.18)
Adalimumab 40mg	1.68 (1.42 – 2.01)	1.35 (1.22 – 1.53)	2.04 (1.43 – 2.91)	1.33 (1.23 – 1.45)	1.17 (1.11 – 1.25)	1.38 (1.19 – 1.66)	0.98 (0.89 – 1.08)	1.06 (0.49 – 2.33)	1.22 (0.54 – 2.78)
Etanercept 50mg BIW	2.14 (1.55 – 2.79)	1.64 (1.41 – 1.89)	3.57 (1.37 – 7.94)	1.58 (1.42 – 1.75)	1.18 (1.11 – 1.27)	1.77 (1.35 – 2.27)	0.96 (0.85 – 1.08)	1.35 (0.53 – 3.45)	1.01 (0.37 – 2.81)
Etanercept 50mg QW	5.61 (3.08 – 10.14)	2.60 (1.81 – 3.80)	5.87 (1.09 – 39.75)	2.67 (2.01 – 3.71)	1.49 (1.27 – 1.80)	4.02 (2.29 – 6.95)	1.09 (0.88 – 1.37)	1.00 (0.29 – 4.00)	2.04 (0.55 – 7.14)
Etanercept 25mg BIW	3.83 (2.38 – 6.27)	2.37 (1.79 – 3.14)	-	2.17 (1.72 – 2.71)	1.40 (1.24 – 1.62)	-	-	-	0.78 (0.14 – 5.32)

Key: AE, adverse event; BIW, biweekly; DLQI, Dermatology Life Quality Index; IGA/PGA, Investigator's Global Assessment/Physician's Global Assessment; PASI, Psoriasis Area Severity Index; SAE, serious adverse event; WDAE, withdrawal due to adverse event; QW, once weekly.

Table 16: Adverse events breakdown for the NAVIGATE trial

	Week 16-40					
	Guselkumab (randomised) n=135			Ustekinumab (randomised) N=133		
AE/ infection, n (%) SOC / preferred term	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**
Infections and infestations	42 (31.1)	0	-	29 (21.8)	1 (0.8)	-
Nasopharyngitis	18 (13.3)	0	-	13 (9.8)	1 (0.8)	-
Upper respiratory tract infection	10 (7.4)	-	-	5 (3.8)	-	-
Sinusitis	3 (2.2)	-	-	0	-	-
Bronchitis	2 (1.5)	-	-	0	-	-
Cystitis	2 (1.5)	-	-	0	-	-
Tinea pedis	2 (1.5)	-	-	0	-	-
Bronchitis viral	1 (0.7)	-	-	0	-	-
Cystitis bacterial	1 (0.7)	-	-	0	-	-
Ear Folliculitis infection	1 (0.7)	-	-	0	-	-
Fungal infection	1 (0.7)	-	-	0	-	-
Gastroenteritis	1 (0.7)	-	-	0	-	-
Gastroenteritis viral	1 (0.7)	-	-	0	-	-
Gastrointestinal viral infection	1 (0.7)	-	-	2 (1.5)	-	-
Genital infection	1 (0.7)	-	-	0	-	-
Gingivitis	1 (0.7)	-	-	0	-	-
Hordeolum	1 (0.7)	-	-	0	-	-
Kidney infection	1 (0.7)	-	-	0	-	-
Lice infestation	1 (0.7)	-	-	0	-	-
Oral herpes	1 (0.7)	-	-	0	-	-
Pulpitis dental	1 (0.7)	-	-	1 (0.8)	-	-

	Week 16-40					
	Guselkumab (randomised) n=135			Ustekinumab (randomised) N=133		
AE/ infection, n (%) SOC / preferred term	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**
Urinary tract infection	1 (0.7)	-	-	1 (0.8)	-	-
Furuncle	0	-	-	1 (0.8)	-	-
Helicobacter infection	0	-	-	1 (0.8)	-	-
Herpes virus infection	0	-	-	1 (0.8)	-	-
Infected dermal cyst	0	-	-	1 (0.8)	-	-
Lower respiratory tract infection	0	-	-	1 (0.8)	-	-
Otitis media	0	-	-	1 (0.8)	-	-
Pharyngitis	0	-	-	1 (0.8)	-	-
Skin candida	0	-	-	1 (0.8)	-	-
Tooth infection	0	-	-	2 (1.5)	-	-
Viral pharyngitis	0	-	-	1 (0.8)	-	-
Viral upper respiratory tract infection	0	-	-	2 (1.5)	-	-
Wound infection	0	-	-	1 (0.8)	-	-
General disorders and administration site conditions	14 (10.4)	1 (0.7)	-	3 (2.3)	0	-
Injection site erythema	3 (2.2)	-	-	0	-	-
Pain	3 (2.2)	-	-	0	-	-
Injection site swelling	2 (1.5)	-	-	0	-	-
Pyrexia	2 (1.5)	-	-	1 (0.8)	-	-
Application site vesicles	1 (0.7)	-	-	0	-	-
Chest pain	1 (0.7)	-	-	2 (1.5)	-	-
Fatigue	1 (0.7)	-	-	0	-	-
Injection site nodule	1 (0.7)	-	-	0	-	-

	Week 16-40					
	Guselkumab (randomised) n=135			Ustekinumab (randomised) N=133		
AE/ infection, n (%) SOC / preferred term	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**
Paradoxical drug reaction	1 (0.7)	1 (0.7)	-	0	0	-
Xerosis	1 (0.7)	-	-	0	-	-
Influenza like illness	0	-	-	1 (0.8)	-	-
Musculoskeletal and connective tissue disorders	14 (10.4)	0	1 (0.7)	7 (5.3)	2 (1.5)	0
Arthralgia	3 (2.2)	-	-	0	-	-
Back pain	3 (2.2)	-	-	3 (2.3)	-	-
Psoriatic arthropathy	3 (2.2)	-	1 (0.7)	1 (0.8)	-	0
Musculoskeletal pain	2 (1.5)	-	-	1 (0.8)	-	-
Arthritis	1 (0.7)	-	-	0	-	-
Bursitis	1 (0.7)	-	-	0	-	-
Flank pain	1 (0.7)	-	-	0	-	-
Intervertebral disc disorder	1 (0.7)	-	-	0	-	-
Joint effusion	1 (0.7)	-	-	0	-	-
Muscle spasms	1 (0.7)	-	-	0	-	-
Muscle tightness	1 (0.7)	-	-	0	-	-
Myalgia	1 (0.7)	-	-	0	-	-
Osteoporosis	1 (0.7)	-	-	0	-	-
Foot deformity	0	0	-	1 (0.8)	1 (0.8)	-
Osteoarthritis	0	-	-	1 (0.8)	-	-
Pain in extremity	0	0	-	1 (0.8)	1 (0.8)	-
Injury, poisoning and procedural complications	11 (8.1)	-	1 (0.7)	8 (6.0)	-	0

	Week 16-40					
	Guselkumab (randomised) n=135			Ustekinumab (randomised) N=133		
AE/ infection, n (%) SOC / preferred term	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**
Arthropod bite	1 (0.7)	-	-	1 (0.8)	-	-
Bone contusion	1 (0.7)	-	-	0	-	-
Contusion	1 (0.7)	-	-	0	-	-
Hand fracture	1 (0.7)	-	-	0	-	-
Laceration	1 (0.7)	-	-	1 (0.8)	-	-
Muscle strain	1 (0.7)	-	-	0	-	-
Scratch	1 (0.7)	-	-	0	-	-
Spinal compression fracture	1 (0.7)	-	-	0	-	-
Thoracic vertebral fracture	1 (0.7)	-	-	0	-	-
Tooth fracture	1 (0.7)	-	-	1 (0.8)	-	-
Toxicity to various agents	1 (0.7)	-	1 (0.7)	0	-	0
Wound	1 (0.7)	-	-	0	-	-
Joint dislocation	0	-	-	1 (0.8)	-	-
Limb injury	0	-	-	1 (0.8)	-	-
Skin abrasion	0	-	-	2 (1.5)	-	-
Sunburn	0	-	-	1 (0.8)	-	-
Investigations	8 (5.9)	1 (0.7)	0	5 (3.8)	0	1 (0.8)
Weight increased	2 (1.5)	-		0	-	
Aspartate aminotransferase increased	1 (0.7)	-	-	0	-	-
Blood creatinine increased	1 (0.7)	-	-	0	-	-
Blood glucose abnormal	1 (0.7)	-	-	0	-	-
Heart rate irregular	1 (0.7)	-	-	0	-	-

	Week 16-40					
	Guselkumab (randomised) n=135			Ustekinumab (randomised) N=133		
AE/ infection, n (%) SOC / preferred term	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**
Hepatic enzyme increased	1 (0.7)	1 (0.7)	0	2 (1.5)	0	1 (0.8)
Neutrophil count abnormal	1 (0.7)	-	-	0	-	-
Intraocular pressure increased	0	-	-	1 (0.8)	-	-
Liver function test abnormal	0	-	-	1 (0.8)	-	-
Platelet count decreased	0	-	-	1 (0.8)	-	-
White blood cell count decreased	0	-	-	1 (0.8)	-	-
Respiratory, thoracic and mediastinal disorders	8 (5.9)	-	-	8 (6.0)	-	-
Cough	4 (3.0)	-	-	3 (2.3)	-	-
Asthma	1 (0.7)	-	-	0	-	-
Chronic obstructive pulmonary disease	1 (0.7)	-	-	0	-	-
Dyspnoea exertional	1 (0.7)	-	-	0	-	-
Sinus congestion	1 (0.7)	-	-	1 (0.8)	-	-
Sleep apnoea syndrome	1 (0.7)	-	-	0	-	-
Epistaxis	0	-	-	1 (0.8)	-	-
Oropharyngeal pain	0	-	-	3 (2.3)	-	-
Gastrointestinal disorders	6 (4.4)	-	-	5 (3.8)	-	-
Diarrhoea	3 (2.2)	-	-		-	-
Abdominal pain	1 (0.7)	-	-	0	-	-
Dental caries	1 (0.7)	-	-	0	-	-
Gastritis	1 (0.7)	-	-	1 (0.8)	-	-
Toothache	1 (0.7)	-	-	1 (0.8)	-	-

	Week 16-40					
	Guselkumab (randomised) n=135			Ustekinumab (randomised) N=133		
AE/ infection, n (%) SOC / preferred term	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**
Dry mouth	0	-	-	1 (0.8)	-	-
Gastroesophageal reflux disease	0	-	-	1 (0.8)	-	-
Loose tooth	0	-	-	1 (0.8)	-	-
Nausea	0	-	-	1 (0.8)	-	-
Vomiting	0	-	-	1 (0.8)	-	-
Metabolism and nutrition disorders	5 (3.7)	-	-	4 (3.0)	-	-
Dehydration	1 (0.7)	-	-	0	-	-
Diabetes mellitus	1 (0.7)	-	-	1 (0.8)	-	-
Gout	1 (0.7)	-	-	0	-	-
Hyperglycaemia	1 (0.7)	-	-	1 (0.8)	-	-
Hyperuricaemia	1 (0.7)	-	-	0	-	-
Iron deficiency	1 (0.7)	-	-	0	-	-
Type 2 diabetes mellitus	1 (0.7)	-	-	0	-	-
Abnormal loss of weight	1 (0.7)	-	-	1 (0.8)	-	-
Hypercholesterolaemia	1 (0.7)	-	-	1 (0.8)	-	-
Skin and subcutaneous tissue disorders	5 (3.7)	-		13 (9.8)	-	
Pruritus	2 (1.5)	-	-	2 (1.5)	-	-
Dermal cyst	1 (0.7)	-	-	1 (0.8)	-	-
Dermatitis contact	1 (0.7)	-	-	0	-	-
Intertrigo	1 (0.7)	-	-	0	-	-
Acne	0	-	-	1 (0.8)	-	-
Alopecia	0	-	-	1 (0.8)	-	-

	Week 16-40					
	Guselkumab (randomised) n=135			Ustekinumab (randomised) N=133		
AE/ infection, n (%) SOC / preferred term	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**
Dermatitis	0	-	-	1 (0.8)	-	-
Hidradenitis	0	-	-	1 (0.8)	-	-
Hyperhidrosis	0	-	-	1 (0.8)	-	-
Night sweats	0	-	-	1 (0.8)	-	-
Polymorphic light eruption	0	-	-	1 (0.8)	-	-
Pruritus generalised	0	-	-	1 (0.8)	-	-
Rash	0	-	-	1 (0.8)	-	-
Urticaria	0	-	-	1 (0.8)	-	-
Vitiligo	0	-	-	1 (0.8)	-	-
Cardiac disorders	4 (3.0)	2 (1.5)	-	3 (2.3)	1 (0.8)	-
Coronary artery disease	2 (1.5)	1 (0.7)	-	0	0	-
Myocardial infarction	2 (1.5)	2 (1.5)	-	0	0	-
Angina unstable	1 (0.7)	1 (0.7)	-	0	0	-
Left ventricular dysfunction	1 (0.7)	-	-	0	-	-
Sinus bradycardia	1 (0.7)	-	-	0	-	-
Tachycardia	1 (0.7)	-	-	0	-	-
Acute myocardial infarction	0	0	-	1 (0.8)	1 (0.8)	-
Atrial fibrillation	0	-	-	1 (0.8)	-	-
Atrioventricular block first degree	0	-	-	1 (0.8)	-	-
Nervous system disorders	3 (2.2)	-	-	5 (3.8)	-	-
Headache	3 (2.2)	-	-	4 (3.0)	-	-
Paraesthesia	0	-	-	1 (0.8)	-	-

	Week 16-40					
	Guselkumab (randomised) n=135			Ustekinumab (randomised) N=133		
AE/ infection, n (%) SOC / preferred term	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**
Psychiatric disorders	3 (2.2)	-	-	4 (3.0)	-	-
Depression	1 (0.7)	-	-	0	-	-
Listless	1 (0.7)	-	-	0	-	-
Major depression	1 (0.7)	-	-	0	-	-
Insomnia	0	-	-	2 (1.5)	-	-
Libido decreased	0	-		1 (0.8)	-	-
Loss of libido	0	-	-	1 (0.8)	-	-
Vascular disorders	3 (2.2)	-	-	3 (2.3)	-	-
Hypertension	3 (2.2)	-	-	2 (1.5)	-	-
Hypertensive crisis	0	0	-	1 (0.8)	1 (0.8)	-
Eye disorders	2 (1.5)	-	-	3 (2.3)	-	-
Cataract	1 (0.7)	-	-	0	-	-
Dry eye	1 (0.7)	-	-	0	-	-
Conjunctivitis allergic	0	-	-	1 (0.8)	-	-
Ocular hyperaemia	0	-	-	1 (0.8)	-	-
Vision blurred	0	-	-	1 (0.8)	-	-
Immune system disorders	2 (1.5)	-	-	1 (0.8)	-	-
Allergy to arthropod sting	1 (0.7)	-	-	0	-	-
Seasonal allergy	1 (0.70	-	-	1 (0.8)	-	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.5)	-	1 (0.7)	1 (0.8)	-	0
Pyogenic granuloma	1 (0.7)	-	-	0	-	-
Transitional cell carcinoma	1 (0.7)	-	1 (0.7)	0	-	0

	Week 16-40					
	Guselkumab (randomised) n=135			Ustekinumab (randomised) N=133		
AE/ infection, n (%) SOC / preferred term	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**
Haemangioma	0	-	-	1 (0.8)	-	-
Renal and urinary disorders	2 (1.5)	-	-	0	-	-
Haematuria	1 (0.7)	-	-	0	-	-
Nephrolithiasis	1 (0.7)	-	-	0	-	-
Blood and lymphatic system disorders	1 (0.7)	-	0	3 (2.3)	-	1 (0.8)
Lymphopenia	1 (0.7)	-	-	0	-	-
Anaemia	0	-	0	2 (1.5)	-	1 (0.8)
Leukopenia	0	-		1 (0.8)	-	
Congenital, familial and genetic disorders	1 (0.7)	-	-	0	-	-
Type V hyperlipidaemia	1 (0.7)	-	-	0	-	-
Ear and labyrinth disorders	1 (0.7)	-	-	0	-	-
Vertigo	1 (0.7)	-	-	0	-	-
Hepatobiliary disorders	1 (0.7)	-	-	2 (1.5)	-	-
Cholelithiasis	1 (0.7)	-	-	1 (0.8)	-	-
Hepatic function abnormal	0	-	-	1 (0.8)	-	-
Pregnancy, puerperium and perinatal conditions	1 (0.7)	-	-	0	-	-
Ectopic pregnancy	1 (0.7)	-	-	0	-	-
Reproductive system and breast disorders	1 (0.7)	-	-	2 (1.5)	-	-
Breast cyst	1 (0.7)	-	-	0	-	-

	Week 16-40					
	Guselkumab (randomised) n=135			Ustekinumab (randomised) N=133		
AE/ infection, n (%) SOC / preferred term	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**	**Incidence (all grades)**	**Incidence (Grade 3+)**	**Resulted in withdrawal**
Cervix inflammation	0	-	-	1 (0.8)	-	-
Dysmenorrhoea	0	-	-	1 (0.8)	-	-
Social circumstances	1 (0.7)	-	-	1 (0.8)	-	-
Pregnancy of partner	1 (0.7)	-	-	1 (0.8)	-	-
Endocrine disorders	0	-	-	1 (0.8)	-	-
Hypothyroidism	0	-	-	1 (0.8)	-	-
Key: AE, adverse event; SOC, system organ class.						

Section B: Clarification on cost-comparison analysis

B1. **PRIORITY QUESTION**: Please provide the England and Wales market share data (n patients, or if n patients is not available % market share) for ixekizumab, secukinumab, ustekinumab, infliximab, adalimumab, etanercept and other drug treatments separately for each of the past 36 months (in one table, see below), also stating the date that the latest full month market share data relates to. If monthly quantities are not available, please provide the most disaggregate format that is; e.g., quarterly, including the Jul-Sep 2017 quarter.

- Please outline whether this market share data is specific to people with severe plaque psoriasis (as defined in the NICE technology appraisal recommendations for biologics), moderate to severe plaque psoriasis, plaque psoriasis or a wider patient group. Was it specific to people who were intolerant or contraindicated to, or whose psoriasis had not responded to, standard systemic therapies (ciclosporin, methotrexate and PUVA)?

In the market share data that were supplied in the submission, dermatologists reported on moderate to severe psoriasis patients who were treated with biologic therapy. Although the questionnaire did not specify to provide patients who were intolerant or contraindicated to, or whose psoriasis had not responded to, standard systemic therapies, the dermatologists were requested to report patients that were treated with biologics and biologics are only indicated in this population.

- How were the 40 dermatologists selected for the market share analysis?

Screening criteria below:

- Dermatologists from the universe of prescribing doctors in the UK are sent out invitation to participate in the survey
- Respondents are screened based on number of years in practice (3-35 years) and patient workload (treated at least 6 Psoriasis patients with biologic therapy in the last 90 days)
- They must be able to make dynamic treatment decisions involving biologic treatment i.e. actively involved in initiation / switch for therapy decisions for using biologic or novel oral treatment with similar treatment profile (including paediatric indication)
- Must spend 50% or more of their time in NHS setting

- Are the psoriasis patients reported by the company restricted to only NHS patients?

Dermatologists were required to spend the majority of their time in NHS setting, however it is not necessary that all psoriasis patients that they reported were NHS patients as some of the patients may have come from their private consultations.

- What makes these patients representative of NHS practice as a whole?

The sample does include a representative sample that is aligned to population distribution in the UK. The clinicians selected need to spend most their time working in the NHS setting (≥ 50% of their time).

This information can be supplied within an excel spreadsheet if this is simpler.

The total biologic market share is summarised in [redacted].

[redacted]

Data is further broken down in Table 17.

Table 17: Number of patients per treatment and wave (August 2014-October 2017), results from a survey of 40 dermatologists prescribing for psoriasis

# Psoriasis patients - Dermatologists	**Wave 1**	**Wave 2**	**Wave 3**	**Wave 4**	**Wave 5**	**Wave 6**	**Wave 7**	**Wave 8**	**Wave 9**	**Wave 10**	**Wave 11**	**Wave 12**	**Wave 13**
	Aug – Oct 2014	Oct – Dec 2014	Mar - Apr 2015	May – Jun 2015	Aug – Oct 2015	Jan - Feb 2016	Mar - May 2016	May – Jun 2016	Aug – Oct 2016	Jan – Feb 2017	Mar - Apr 2017	May – Jul 2017	Sep - Oct 2017
Taltz (ixekizumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cosentyx (secukinumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stelara (ustekinumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remicade & biosimilars (infliximab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Humira (adalimumab)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enbrel & biosimilars (etanercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B2. **PRIORITY QUESTION**: The analysis includes a response assessment at week 16, to determine whether the treatment stops or continues. Do the costings for adalimumab assume that response is assessed before or after the week 16 dose has been administered? That is, do all patients receive 1*80mg dose and 7*40mg doses or 8*40mg doses?

In the schedule by which costs are calculated for adalimumab a loading dose 80mg is applied at baseline (cycle zero in the model). The first subsequent administration follows one week later, with thereafter one administration every other week. This amounts to 8*40mg doses prior to the response assessment implemented after 16 weeks.

- Administered weeks 0 (80mg), 1, 3, 5, 7, 9, 11, 13, and 15 (40mg) to all patients.
- Administered week 17 (40mg) to responders, and thereafter responders net of discontinuation.

B3. **PRIORITY QUESTION**: Please tabulate the input values that are changed from the base case for the sensitivity analysis "Probability of initial response at the end of induction period (all therapies)". Please provide the rationale for the values used in this sensitivity analysis.

Tabulation of changed input values is provided in Table 18. The analysis adopted an assumption of an arbitrary 20% variation either side of the mean, but constrained the upper limit to 1.00. In view of this question, however, we looked back to the source analysis that produced the point estimate, and retrieved the associated 95% credible interval [0.7742 to 0.8822]. Clearly this is a narrower range of uncertainty than represented in our submission. We include below results of the sensitivity analysis when the range is set based on the credible interval. As shown in Table 18 these credible intervals reduce the impact on base case cost savings when guselkumab is compared to ustekinumab, but have little impact when comparing against adalimumab.

Table 18: Input values that are changed from the base case for the sensitivity analysis "Probability of initial response at the end of induction period (all therapies)"

Parameter	Value	Cost difference 5 years	
		vs adalimumab	vs ustekinumab
Base case	[redacted]	[redacted]	[redacted]
Lower range (submission)	0.6678	[redacted]	[redacted]
Upper range (submission)	1.0000	[redacted]	[redacted]
Lower range (credible interval)	0.7742	[redacted]	[redacted]
Upper range (credible interval)	0.8822	[redacted]	[redacted]

B4. **PRIORITY QUESTION**: Janssen funds a homecare service for those who cannot self-inject.

a. Please provide more detail of what this funds, the annual funding per patient or per patient visit, whether this is NHS or private sector nurses and how this funding is arranged.

[redacted]

b. What proportion of people with plaque psoriasis receiving ustekinumab in the UK require this service? If this cannot be provided specific to people with plaque psoriasis, please provide it for the smallest patient group that encompasses these patients.

[redacted]

c. If Janssen is aware of any comparator companies providing a similar self-injection service, please provide details of these.

Most competitors offer home delivery, some offer the self-injection training service, none that we are aware off offer the ongoing nurse administration service.

B5. The company's assumption of a 20% discontinuation rate for all 3 treatments in its cost comparison analysis does not reflect real world discontinuation rates reported by Arnold et al. (2016), Menter (2016), Warren (2015). These suggest higher discontinuation for adalimumab (~20%/year) than for ustekinumab (~8%/year). Please explain how using different annual withdrawal rates for each comparator might alter the results of the cost-comparison, and how this might interplay with treatment sequence?

The submitted cost comparison model addresses the total costs for each biologic over 5 years based on specific scheduling of administration in given cycles. For the purposes of the Fast Track Appraisal approach, the model assumes comparable rates of discontinuation. In practice, patients will sequence through biologic therapies, and as question B5 highlights discontinuation rates may differ among biologics, even if efficacy across the biologics is considered comparable. Sequencing options will differ according to the availability of guselkumab.

Table 19 summarises expected total costs per annum in the absence of discontinuation.

[redacted]

Table 19: Annual expected costs excluding discontinuation

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

With respect to the potential impact of differential rates of discontinuation, question B5 suggests a scenario with a potentially lower rate of discontinuation per annum for guselkumab compared to adalimumab. In considering the implications of this in a sequencing context we note the following:

- Psoriasis is a chronic condition and patients are expected to spend years in maintenance (Menter et al.[7]), [redacted]

- In clinical practice patients who discontinue due to lack of efficacy or intolerance move to another biologic, which can be expected to be one with a similar cost and efficacy profile to the initial biologic (The cost of biologics is broadly comparable and range between £9,000-£11,000 per year).

- For a patient treated with guselkumab post-discontinuation, therapy options include adalimumab and ustekinumab, while patients initiated on either adalimumab or ustekinumab, in the absence of ustekinumab, may be expected to switch from one to the other.

- Where patients discontinue adalimumab, we could therefore assume they move to ustekinumab with expected first year cost (excluding further discontinuation) of £10,735 followed by maintenance at £9,304 per annum. With lower discontinuation rates than for adalimumab where a patient is initially treated with guselkumab the ongoing cost will be [redacted], which is [redacted] than either the expected induction or maintenance cost for ustekinumab following adalimumab discontinuation.

- Where patients discontinue ustekinumab we could also assume they move to adalimumab (less costly than ustekinumab), with expected first year cost of £9,684, followed by maintenance at £9,156 per annum. Patients initially treated with guselkumab may discontinue at a more comparable rate to those treated with ustekinumab, and also have the option of a move to adalimumab; however, in this case acquisition costs in first line will have been [redacted] due to the difference in expected costs between guselkumab and ustekinumab (Table 19).

- Cost comparison requires that the cost of the appraised technology is similar to or lower than the comparator technologies over the course of the relevant time horizon, in this case, 5 years. This is clearly demonstrated in the table above. In a sequencing context this cost comparability can be expected to be maintained

beyond a point of first biologic discontinuation, irrespective of potentially dissimilar discontinuation rates.

Section C: Textual clarifications and additional points

C1. There appears to be a typo about NAVIGATE on pages 163-4 of the appendices. Current statement: “Patients who responded to initial ustekinumab therapy were randomised to receive either guselkumab or ustekinumab”. Please confirm that this should read: “Patients who didn’t respond to initial ustekinumab therapy were randomised to receive either guselkumab or ustekinumab”.

We can confirm that this should read “Patients who didn’t respond to initial ustekinumab therapy were randomised to receive either guselkumab or ustekinumab”.

C2. Mortality as an outcome is not addressed in this submission. Please update Table 1 (“Decision Problem”) in Document B of the company submission accordingly.

An updated outcome row for Table 1 of Document B is provided as Table 20.

Table 20: Revised outcomes summary for the decision problem table

Outcomes	The outcome measures to be considered include: • Severity of psoriasis • Psoriasis symptoms on the face, scalp and nails • Response and remission rate • Relapse rate • Mortality • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Severity of psoriasis • Psoriasis symptoms on the face, scalp and nails • Response and remission rate (as represented by skin clearance) • Relapse rate (as represented by loss of response) • Adverse effects of treatment • Health-related quality of life	Mortality data were not collected in the guselkumab clinical development programme.

C3. Please confirm the duration of induction with guselkumab and when the first maintenance dose is administered. Table 7 of the appendix state that the induction period in the VOYAGE trials was 16 weeks, however some descriptions of the dosing schedule imply that the first maintenance dose is administered at week 12. Please clarify.

The induction period of the VOYAGE trials involved dosing of guselkumab at Weeks 0, 4 and 12 for patients randomised to guselkumab at baseline. The first maintenance dose was administered at Week 20 and every 8 weeks thereafter.

Primary endpoint analyses for the induction period were conducted at Week 16, that is, four weeks after completion of all three induction doses (Weeks 0, 4 and 12).

C4. Pages 102–3 of the company submission refer to only ustekinumab as a comparator. Please confirm that adalimumab should have been included in these statements.

We can confirm that adalimumab should have been included in these statements.

References

1. Janssen Research & Development LLC. Summary of Product Characteristics. Stelara (ustekinumab) 16 January 2009. Available at: http://www.medicines.org.uk/emc/medicine/32569. Accessed: 11 September 2017.
2. Langley RG, Feldman SR, Nyirady J, et al. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. *J Dermatolog Treat*. 2015; 26(1):23-31.
3. Kim GK and Del Rosso JQ. Drug-Provoked Psoriasis: Is It Drug Induced or Drug Aggravated?: Understanding Pathophysiology and Clinical Relevance. *The Journal of clinical and aesthetic dermatology*. 2010; 3(1):32-8.
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5. The Royal College of Psychiatrists. Medications for Bipolar Disorder. 2017. Available at: http://www.rcpsych.ac.uk/healthadvice/treatmentswellbeing/medicationsbipolardisorder.aspx. Accessed: 24 November 2017.
6. Kimball AB, Leonardi C, Stahle M, et al. Demography, baseline disease characteristics and treatment history of patients with psoriasis enrolled in a multicentre, prospective, disease-based registry (PSOLAR). *Br J Dermatol*. 2014; 171(1):137-47.
7. Menter A, Papp KA, Gooderham M, et al. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Eur Acad Dermatol Venereol*. 2016; 30(7):1148-58.

A5. **PRIORITY QUESTION**: The ERG would like to know how many centres and investigators were common to both Voyage 1 and 2 (and Navigate if possible) to see if they are truly two different trials.

Janssen reviewed the available information on the clinical trial centres for the three clinical trials - VOYAGE 1 (NCT02207231), VOYAGE 2 (NCT02207244) and NAVIGATE (NCT02203032). Janssen can confirm that these are three different clinical trials. The proportion of centres common across trials and details of centre participation by region, country and trial are provided in Table 1 and

Table 2 respectively.

As shown in Table 1, more than half (54%) of the centres participated in one trial, Voyage 1, Voyage 2 or Navigate. Less than half participated in two trials (38.5%) or three trials (7.5%). Within the centres that participated in more than one trial, different combinations were observed Voyage 1 + 2 (15.5%), Voyage 1 + Navigate (12.8%) and Voyage 2 + Navigate (13.4%). Please see the details of centre participation by trial and region in

Table 2.

Table 1 Number and proportion of sites participating in 1, 2 and 3 trials.

Number of trials	Number of sites	Proportion
1 trial	101	54.0%
2 trials	72	38.5%
Voyage 1 and Voyage 2	29	15.5%
Voyage 1 and Navigate	24	12.8%
Voyage 2 and Navigate	25	13.4%
3 trials	14	7.5%

Table 2 Centre participation by region, country and trial.

VOYAGE 1	VOYAGE 2	NAVIGATE
North America		
Canada		
	CA00174	
		CA00182
	CA00185	
CA00244		
		CA00245
CA00246		
CA00247		
		CA00248
	CA00249	

CA00250		
	CA00251	
	CA00252	
CA00253		
CA00254		
	CA00264	
CA00281		CA00281
		CA00288
CA00289		
	CA00290	
	CA00291	
CA90077		CA90077
CA90165		CA90165
CA90202		
		CA90210
	CA90097	
	CA90210	
United States		
US00494		US00494
US01499		US01499
US01500	US01500	US01500
	US01502	US01502
	US01503	US01503
US01505		US01505
		US01506
US01507	US01507	
	US01510	
US01511	US01511	US01511
US01512	US01512	
US01513	US01513	
US02019		
US02020		US02020
US02021	US02021	US02021
US02022	US02022	
US02046		US02046
	US02047	
	US02051	
US02052	US02052	
	US02071	

		US02073
US02074		US02074
	US02111	US02111
	US02138	
US02139		US02139
		US02140
US02260		
US02275	US02275	US02275
	US02328	US02328
	US02329	
US90232		
	US02347	
	US02348	US02348
		US02350
		US90232
US90807		
	US91481	
US91488		US91488
US91491	US91491	
	US91507	US91507
US91513		
US91723	US91723	
	US92304	US92304
	US92404	
US92606	US92606	US92606
US93365	US93365	
	US93366	
US93367		
	US93368	
Eastern Europe		
Hungary		
HU36001		
HU36002		
HU36003		
HU36004		
HU36005		
HU36006		
Czech Republic		

	CZ00135	
	CZ00136	
	CZ00137	
	CZ00138	
	CZ90035	
	CZ90039	
	CZ90040	
Poland		
	PL00165	PL00165
	PL00226	PL00226
PL00227	PL00227	PL00227
	PL00228	PL00228
	PL00229	PL00229
PL00230	PL00230	PL00230
	PL00231	PL00231
	PL00232	PL00232
PL00233	PL00233	PL00233
PL00235	PL00235	PL00235
	PL00238	PL00238
	PL00239	PL00239
PL00240	PL00240	PL00241
	PL00242	PL00242
	PL00244	
	PL00245	PL00245
PL00246	PL00246	PL00248
PL00248	PL00248	PL00249
		PL00250
Russia		
RU00366	RU00366	
RU00369	RU00369	
RU00370	RU00370	
RU00371		RU00371
RU00372	RU00372	
RU00374		
RU00375	RU00375	
	RU00377	RU00377
	RU00378	
	RU00379	
	RU00380	

	RU00381	
RU00382		RU00382
		RU90263
RU90279		
RU90282		RU90282
RU90288	RU90288	
RU90310		
Western Europe		
Germany		
DE00292		
DE00480		DE00480
DE00481	DE00481	
DE00482	DE00482	
DE00483		DE00483
DE00485		DE00485
DE00486	DE00486	
	DE00487	DE00487
DE00488	DE00488	
DE00490	DE00489	
DE00491	DE00491	DE00491
DE00492	DE00492	DE00492
DE00493	DE00495	
DE00495		
DE00496		
	DE00500	DE00500
Spain		
ES00516		
		ES00517
ES00523		
		ES00526
ES00538		
ES00541		
ES00542		
	ES00353	
	ES00358	
	ES00519	
	ES00522	
	ES00525	
	ES00530	

	ES00532	
	ES00534	
	ES00539	
Asia Pacific		
Australia		
	AU00212	
AU00213	AU00213	
		AU00216
AU00217		
	AU00218	
	AU00219	
AU00220		AU00220
AU00254		
AU00255		
South Korea		
	KR00149	KR00149
	KR00150	KR00150
	KR00151	
	KR00152	
	KR00153	KR00153
		KR00154
KR00155	KR00155	
KR00156	KR00156	
KR00157	KR00157	
KR00158	KR00158	
KR00160	KR00159	
KR00161	KR00160	
	KR00161	
	KR00162	
Taiwan		
TW00035		TW00035
TW00061		
TW00076		TW00076
TW00077		TW00077
TW00078		
TW90068		TW90068

A9. **PRIORITY QUESTION**: Please outline the arithmetic used to derive the following outcomes for placebo, guselkumab, ustekinumab and adalimumab from the central estimates in Table 14 of Document B: PASI75, PASI90, PASI100, DLQI 0/1 and SAEs. This can be supplied in an excel spreadsheet.

The following arithmetic was used to derive the probability of a treatment achieving a given outcome, where a baseline value was assumed for placebo, based on studies with a placebo arm for a given outcome:

$$p_{Treatment} = \exp\{\ln(RR_{Treatment\ vs.Placebo}) + \ln(p_{Placebo})\}$$

$$where\ p_{Treatment} = probabiblity\ of\ treatment\ achieving\ outcome,$$

$$p_{Placebo} = probability\ of\ placebo\ achieving\ outcome$$

$$RR_{Treatment\ vs.Placebo} = \frac{probabiblity\ of\ treatment\ achieving\ outcome}{probability\ of\ placebo\ achieving\ outcome}$$

$$where\ RR_{Treatment\ vs.Placebo} = Risk\ Ratio\ of\ Treatment\ versus\ Placebo$$

$\ln(p_{Placebo})$ is estimated from the NMA model from a normal distribution from a mean (μ) which is the mean estimated from all the studies with placebo arm for a given outcome, and a precision ($\tau = \frac{1}{standard\ deviation^2}$) of μ from all the studies with placebo arms for a given outcome:

$$\ln(p_{Placebo}) \sim Normal(\mu, \tau)$$

For example, PASI 75 the $p_{Placebo}$ is estimated to be 0.051 (i.e. 5.10%) from the NMA model, therefore if we want to calculate the probability of achieving PASI 75 for guselkumab, adalimumab, and ustekinumab using the central values (i.e. risk ratios) versus placebo from Table 14 and Figure 14, it's as follows:

[redacted]

Additional detail is available within the WinBUGS code provided (which is based on NICE Technical Support Document Series: https://scharr.dept.shef.ac.uk/nicedsu/technical-support-documents/evidence-synthesis-tsd-series/)

A9. **PRIORITY QUESTION**: Please outline the arithmetic used to derive the following outcomes for placebo, guselkumab, ustekinumab and adalimumab from the central estimates in Table 14 of Document B: PASI75, PASI90, PASI100, DLQI 0/1 and SAEs. This can be supplied in an excel spreadsheet.

The following arithmetic was used to derive the probability of a treatment achieving a given outcome, where a baseline value was assumed for placebo, based on studies with a placebo arm for a given outcome:

$$p_{Treatment} = \exp\{\ln(RR_{Treatment\ vs.Placebo}) + \ln(p_{Placebo})\}$$

$$where\ p_{Treatment} = probability\ of\ treatment\ achieving\ outcome,$$

$$p_{Placebo} = probability\ of\ placebo\ achieving\ outcome$$

$$RR_{Treatment\ vs.Placebo} = \frac{probability\ of\ treatment\ achieving\ outcome}{probability\ of\ placebo\ achieving\ outcome}$$

$$where\ RR_{Treatment\ vs.Placebo} = Risk\ Ratio\ of\ Treatment\ versus\ Placebo$$

$\ln(p_{Placebo})$ is estimated from the NMA model from a normal distribution from a mean (μ) which is the mean estimated from all the studies with placebo arm for a given outcome, and a precision ($\tau = \frac{1}{standard\ deviation^2}$) of μ from all the studies with placebo arms for a given outcome:

$$\ln(p_{Placebo}) \sim Normal(\mu, \tau)$$

For PASI 75, the $p_{Placebo}$ is estimated to be 0.051 (i.e. 5.10%) from the NMA model, therefore if we want to calculate the probability of achieving PASI 75 for guselkumab, adalimumab, and ustekinumab using the central values (i.e. risk ratios) versus placebo it's as follows:

[redacted]

As an example, the relative risk pairwise comparison of guselkumab versus placebo from baseline risk-adjusted relative effects analyses for PASI 75 is [redacted], as displayed in Table 14 of document B.

For PASI 90 the $p_{Placebo}$ is estimated to be 0.0169 (i.e. 1.69%) from the NMA model, therefore if we want to calculate the probability of achieving PASI 90 for guselkumab, adalimumab, and ustekinumab using the central values (i.e. risk ratios) versus placebo it's as follows:

$$p_{Guselkumab\ for\ PASI\ 90} = \exp\{\ln(43.22) + \ln(0.0169)\} = 0.7304\ (73.04\%)$$

$$p_{Adalimumab\ for\ PASI\ 90} = \exp\{\ln(29.24) + \ln(0.0169)\} = 0.4942\ (49.42\%)$$

$$p_{Ustekinumab\ 90\ mg\ for\ PASI\ 90} = \exp\{\ln(28.41) + \ln(0.0169)\} = 0.4801\ (48.01\%)$$

$$p_{Ustekinumab\ 45\ mg\ for\ PASI\ 90} = \exp\{\ln(27.49) + \ln(0.0169)\} = 0.4646\ (46.46\%)$$

$$p_{Ustekinumab\ 45/90\ mg\ for\ PASI\ 90} = \exp\{\ln(26.52) + \ln(0.0169)\} = 0.4482\ (44.82\%)$$

$$p_{placebo\ for\ PASI\ 90} = \exp\{\ln(1) + \ln(0.0169)\} = 0.0169\ (1.69\%)$$

For PASI 100, the $p_{Placebo}$ is estimated to be 0.004435 (i.e. 0.4435%) from the NMA model, therefore if we want to calculate the probability of achieving PASI 100 for guselkumab, adalimumab, and ustekinumab using the central values (i.e. risk ratios) versus placebo it's as follows:

$$p_{Guselkumab\ for\ PASI\ 100} = \exp\{\ln(63.33) + \ln(0.004435\ )\} = 0.2809\ (28.09\%)$$

$$p_{Adalimumab\ for\ PASI\ 100} = \exp\{\ln(32.14) + \ln(0.004435\ )\} = 0.1425\ (14.25\%)$$

$$p_{Ustekinumab\ 90\ mg\ for\ PASI\ 100} = \exp\{\ln(21.23) + \ln(0.004435\ )\} = 0.0942\ (9.42\%)$$

$$p_{Ustekinumab\ 45\ mg\ for\ PASI\ 100} = \exp\{\ln(31.45) + \ln(0.004435\ )\} = 0.1395\ (13.95\%)$$

$$p_{Ustekinumab\ 45/90\ mg\ for\ PASI\ 100} = \exp\{\ln(34.55) + \ln(0.004435\ )\} = 0.1532\ (15.32\%)$$

$$p_{placebo\ for\ PASI\ 100} = \exp\{\ln(1) + \ln(0.004435\ )\} = 0.004435\ (0.4435\%)$$

For DLQI, the $p_{Placebo}$ is estimated to be 0.0671 (i.e. 6.71 %) from the NMA model, therefore if we want to calculate the probability of achieving DLQI for guselkumab, adalimumab, and ustekinumab using the central values (i.e. risk ratios) versus placebo it's as follows:

$$p_{Guselkumab\ for\ DLQI} = \exp\{\ln(8.63) + \ln(0.0671)\} = 0.5791\ (57.91\%)$$

$$p_{Adalimumab\ for\ DLQI} = \exp\{\ln(5.73) + \ln(0.0671)\} = 0.3845\ (38.45\%)$$

$$p_{Ustekinumab\ 90\ mg\ for\ DLQI} = \exp\{\ln(8.74) + \ln(0.0671)\} = 0.5865\ (58.65\%)$$

$$p_{Ustekinumab\ 45\ mg\ for\ DLQI} = \exp\{\ln(8.57) + \ln(0.0671)\} = 0.5751\ (57.51\%)$$

$$p_{Ustekinumab\ 45/90\ mg\ for\ DLQI} = \exp\{\ln(7.12) + \ln(0.0671)\} = 0.4778\ (47.78\%)$$

$$p_{placebo\ for\ DLQI} = \exp\{\ln(1) + \ln(0.0671)\} = 0.0671(6.71\%)$$

For SAE, the $p_{Placebo}$ is estimated to be 0.0223 (i.e. 2.23 %) from the NMA model, therefore if we want to calculate the probability of achieving SAE for guselkumab, adalimumab, and ustekinumab using the central values (i.e. risk ratios) versus placebo it's as follows:

$$p_{Guselkumab\ for\ SAE} = \exp\{\ln(1.05) + \ln(0.0223)\} = 0.0234\ (2.34\%)$$

$$p_{Adalimumab\ for\ SAE} = \exp\{\ln(1.05) + \ln(0.0671)\} = 0.0234\ (2.34\%)$$

$$p_{Ustekinumab\ 90\ mg\ for\ SAE} = \exp\{\ln(0.83) + \ln(0.0223)\} = 0.0185\ (1.85\%)$$

$$p_{Ustekinumab\ 45\ mg\ for\ SAE} = \exp\{\ln(0.73) + \ln(0.0223)\} = 0.0163\ (1.63\%)$$

$$p_{Ustekinumab\ 45/90\ mg\ for\ SAE} = \exp\{\ln(0.74) + \ln(0.0223)\} = 0.0165\ (1.65\%)$$

$$p_{placebo\ for\ SAE} = \exp\{\ln(1) + \ln(0.0223)\} = 0.0223\ (2.23\%)$$

Additional detail is available within the WinBUGS code provided (which is based on NICE Technical Support Document Series: https://scharr.dept.shef.ac.uk/nicedsu/technical-support-documents/evidence-synthesis-tsd-series/)

NICE National Institute for Health and Care Excellence

Patient organisation submission

Guselkumab for treating moderate to severe plaque psoriasis [ID1075]

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

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Psoriasis and Psoriatic Arthritis (PAPAA)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The organisation is a national charity, which provides support, education and training for people affected by both psoriasis and psoriatic arthritis. To meet the changing times, much of our activity is now digital via our main website, which is currently seeing >850,000 page views per year. The organisation provides its services free of charge and therefore does not charge a membership fee. Funding is via donations and other fundraising activities. The charity does not accept any funding from the pharmaceutical industry. A register of support and interest is available to join and currently includes >13,000 people. The register not only includes people with psoriasis and or psoriatic arthritis, but their carers and others interested in both conditions. We also have an active professional database and support this group regularly through the provision of patient support material and an online education programme.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include inyour submission?	We continually gather data via ongoing surveys along with ad hoc topic specific questionnaires. We have an e-newsletter, which provides immediate access to views, and we utilise social media to gain instant views. For this submission, we have used our experience of talking and engaging with people and their carers affected by psoriasis, to give an overview of the current state of their needs and views.

Living with the condition	
6. What is it like to live with the condition?What do carers experience when caring for someone with the condition?	For some people living with psoriasis, the condition is often a mild irritation and has little impact on their lives. Although, it has to be said, there are people with mild psoriasis who find the condition extremely distressing, so the impact of low levels of disease, should not be underestimated. As the condition often flares quickly, those with mild psoriasis can find themselves with a more widespread moderate case, their usual treatments may be difficult to use or appear to become ineffective. The uncertainty of response, rapid onset over a few days has a huge psychological impact and causes individuals to become very self-conscious and often avoid activities where their psoriasis might be obvious or cause embarrassment. People with psoriasis are very aware of the affect that the condition may have on their close family. This is often highlighted by a reluctance to use public changing areas or take part in activities such as swimming. A withdrawal of close contact also can become an issue, with self-loathing adding to the overall burden of living everyday with this disease. Choice of clothing to avoid highlighting the shed skin is another problem, as are visits to public locations, where people often find themselves very aware that their skin is leaving a trail on the surrounding furnishings. Psoriasis can be a lonely disease of constant treatments, remission and then flare, where the anxiety of the return or flare during remission, sometimes being as bad as the condition itself.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	There are mixed views about current therapies. For mild-to-moderate psoriasis, the usual therapies are topical and these generally are disliked. They often are messy, smelly, inconvenient and time consuming. The use of phototherapy although effective is also inconvenient, as it is often needed 2 or 3 times a week over a 6-week period, which for those who work can be difficult to complete. There is also inconsistent and variable access to phototherapy. The use of DMARDs such as methotrexate is also a concern for people as they are apprehensive of the drug and its adverse event profile, loss of hair, reduced immune system and potential liver toxicity are of concern. The latter is often highlighted as a key issue for avoidance of methotrexate, due to the need to avoid or reduce alcohol in-take. This may appear trivial in the scheme of improving psoriasis, but many find this difficult to contemplate. Newer biological agents have been welcomed, and provide people with more convenient therapy, but given the high cost, people often feel they are being blocked or delayed access to what they perceive to be better options.
8. Is there an unmet need for patients with this condition?	There are always going to be people who have lack of efficacy, drug resistance or failures, so a need for further options would be welcomed. Reduced cost of therapies would allow earlier access and potentially avoid the need to try less effective toxic therapies.
Advantages ofthe technology	
9. What do patients or carers think are the advantages of the technology?	As the technology is not routinely available, it is difficult to assess, but it would be hoped that it would provide improved clearance than those of similar class, which are currently being prescribed. Patients want to see clearance of all signs and symptoms of psoriasis, therefore PASI90 and clearance in more people would be seen as an advantage.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The cost would be seen as a barrier, if it delays use. A worse adverse events profile versus other agents that provide similar benefit would be seen as a disadvantage.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	If it could be seen to provide improvement in those with psoriatic arthritis symptoms, that could be seen as a group who may gain a benefit against a therapy that only improves psoriasis alone.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

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

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • Psoriasis is a life long disease • Treatments often fail, so options are needed • The psychological impact can be widespread • Treatment costs need to be reduced, to provide earlier access to more effective drugs • Clearance of all signs and symptoms, should be the goal of any new treatment

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Guselkumab for treating moderate to severe plaque psoriasis [ID1075]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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

About you	
1. Your name	[redacted] on behalf of the Therapy & Guidelines sub-committee and British Association of Dermatologists Biologic Interventions Register (BADBIR) Steering Committee
2. Name of organisation	British Association of Dermatologists

3. Job title or position	**Consultant Dermatologists; chairs, Therapy & Guidelines sub-committee and BADBIR steering committee**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a charity whose charitable objectives are the practice, teaching, training and research of Dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of Dermatology services across all service settings. It is funded by the activities of its Members.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	• Control of psoriasis with the aim of a 'clear' or 'nearly clear' Physician's Global Assessment rating • Reducing the impact of the disease on quality of life •

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Current guidelines (specifically the published 2017 BAD guidelines on biologic therapies for psoriasis, and prior NICE STAs have defined a minimum clinically significant improvement as: • ≥ 50% reduction in baseline disease severity, e.g. a PASI50 response, or percentage BSA where PASI is not applicable, and • Clinically relevant improvement in physical, psychological or social functioning (e.g. ≥ a 4-point improvement in DLQI score or resolution of low mood)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes: 1. In real-world practice, not all people with psoriasis who fulfil NICE criteria for biologic therapy respond to existing biologic therapies; secondary failure is also common (Iskandar IYK, Ashcroft DM, Warren RB, Evans I, McElhone K, Owen CM, Burden AD, Smith CH, Reynolds NJ, Griffiths CEM. Patterns of biologic therapy use in the management of psoriasis: cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). Br J Dermatol. 2017 May;176(5):1297-1307. doi: 10.1111/bjd.15027. Epub 2017 Mar 20. PubMed PMID:27589476; Warren RB, Smith CH, Yiu ZZN, Ashcroft DM, Barker JNWN, Burden AD, Lunt M, McElhone K, Ormerod AD, Owen CM, Reynolds NJ, Griffiths CEM. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J

	Invest Dermatol. 2015 Nov;135(11):2632-2640. doi: 10.1038/jid.2015.208. Epub 2015 Jun 8. PubMed PMID:26053050. 2. In moderate psoriasis, i.e. those who would fulfil the licensed indications for biologic therapy (including guselkumab) there are very few options and yet the disease can still have a very major impact on quality of life 3. People with severe psoriasis at localised sites, i.e. high-need areas such as face, hands, feet, flexural/genital sites, will not have a PASI 10 but nevertheless will have disease with very major impact.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	With NICE-approved biologic therapies and biosimilars; apremilast; fumaric acid esters; standard systemic therapies (see NICE CG153).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes: BAD guideline for biologic therapy for psoriasis http://onlinelibrary.wiley.com/doi/10.1111/bjd.15665/full NICE CG153 www.nice.org.uk/guidance/cg153 Please note the following comments regarding the final scope below ➔ In the final scope, please refer to NICE CG153 accurately (i.e. corticosteroids/vitamin D as first line), also updated in 2016/7 ➔ Phototherapy/systemic therapy for disease that is extensive (10% or more) – i.e. this group cannot usually be managed adequately with topical therapy alone (again please refer to CG153 accurately)

	➔ There should also be mention of psoriatic arthritis as an important, common co-morbidity and that when present, of the standard systemic therapies used in psoriasis, only methotrexate is helpful for both joints and skin. Additionally, the final scope mentions that "most treatments reduce severity rather than prevent episodes" – there is no evidence that any of the treatments are disease-modifying. This would better describe the point being made here (rather than "most treatments reduce severity….") as many of the new biologic treatments do clear or nearly clear the disease and maintain it in this state.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes – please see NICE CG153. Data from BADBIR national pharmacovigilance registry suggest that most people with psoriasis fulfil stipulated criteria, e.g. PASI mean (SD) = 16.4 (8.3) – please see Iskandar IY, Ashcroft DM, Warren RB, Yiu ZZ, McElhone K, Lunt M, Barker JN, Burden AD, Ormerod AD, Reynolds NJ, Smith CH, Griffiths CE. Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. Br J Dermatol. 2015 Aug;173(2):510-8. doi: 10.1111/bjd.13908. Epub 2015 Jul 6. PubMed PMID:25989336.
• What impact would the technology have on the current pathway of care?	An additional option to consider in people with severe psoriasis; an agent with a novel mode of action, i.e. IL23 receptor antagonist. More agents within the same 'market' may provide motivation to drive down the price.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – biologic therapy is a well-established intervention in psoriasis.

• How does healthcare resource use differ between the technology and current care?	There would not be any expected differences in health resource use compared to existing NICE-approved agents.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment would be required.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	N/A

• Do you expect the technology to increase health-related quality of life more than current care?	Potentially yes, by providing an additional treatment option for this major, chronic debilitating disease.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Biologic therapy has been available on the NHS for people with moderate-to-severe psoriasis who meet the eligibility criteria.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The published 2017 BAD guidelines recommended biologic therapy for the following people with psoriasis: Offer biologic therapy to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated (see NICE guidelines CG153) and the psoriasis has a large impact on physical, psychological or social functioning (e.g. Dermatology Life Quality Index [DLQI] or Children's DLQI > 10 or clinically relevant depressive or anxiety symptoms) and one or more of the following disease severity criteria apply: • the psoriasis is extensive [defined as body surface area (BSA) > 10% or Psoriasis Area and Severity Index (PASI) ≥ 10] • the psoriasis is severe at localized sites and associated with significant functional impairment and/or high levels of distress (for example nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures and genitals). These criteria do extend to additional (small) subsets of people with psoriasis currently not covered by the NICE criteria for biologic therapy and were introduced due the limitations of the PASI disease severity tool (i.e. it is strongly dependent on body surface area affected, and for some people with localised disease at high-need sites the PASI will not reach 10) and the specific burden (and limited options) for people with disease in both compartments (skin and joint). Generally, therapy is stopped when: • the minimal response criteria are not met, either initially or further down the line (i.e. secondary failure)

	• adverse effects arise, e.g. development of neurological symptoms suggestive of demyelinating disease, or new/worsening pre-existing heart failure • the risks outweigh the benefits in a) pregnant females or females planning conception and b) people undergoing elective surgery • live vaccines need to be administered No additional testing from what already recommended for biologics.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes: The calculation of the QALY does not encompass time off work or other limitations that psoriasis imposes (e.g. social isolation, avoidance of relationships, stigma, depression, anxiety). Furthermore, the DLQI is often mapped to EQ5D but whilst important, the DLQI doesn't capture anxiety and depression (which are common in psoriasis); we also know that the mapping algorithms are not necessarily accurate (*paper submitted for publication using EQ5D and DLQI data from pharmacovigilance registry BADBIR*)
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	This is the first IL23-only antagonist.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Antagonism of the IL23 pathway represent a step-change in the management of people with moderate-to-severe psoriasis.
• Does the use of the technology address any particular unmet need of the patient population?	Please see response in Q8 above.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Guselkumab seems to have a comparable safety profile with other biologic therapies, although there is currently little data about its safety in a real-world population.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	• **Psoriasis improvement on the face, scalp, nails:** Plus, other high-need sites, i.e. hands and feet, flexural/genital psoriasis. • **Response rate:** Over what time period? It would be important to include longer treatment outcomes, i.e. 1 year, 2 years. • **Relapse rate:** over what time period? It would be important to include longer treatment outcomes, i.e. 1 year, 2 years. • **Adverse effects of treatment:** infection; separate out adverse effects in the very short term, e.g. during loading doses. • **Health-related quality of life (including dermatology quality of life index [DLQI]):** Include other measures of impact, i.e. depression, anxiety; and impact on psoriatic arthritis.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	See notes above.
• Are there any adverse effects that were not apparent in clinical trials	There is very limited information about use of the technology outside clinical trials. It would be extremely important for all people with psoriasis who meet the eligibility criteria to be enrolled in BADBIR when prescribed this agent to

but have come to light subsequently?	ensure capture of high quality pharmacovigilance data and to allow relevant comparisons with other biologic agents (N.B. > 12,000 patients now registered – please see www.badbir.org.uk)
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No; however, ciclosporin cannot be used for > 1 year and is therefore not a relevant comparator for this STA.
21. How do data on real-world experience compare with the trial data?	Not yet available for this technology.
Equality	
22a. Are there any potential equality issues that should be	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).

taken into account when considering this treatment?	DLQI will underestimate the impact in people who are not sexually active, or older (retired) or socially isolated; it does not capture anxiety and depression.
22b. Consider whether these issues are different from issues with current care and why.	These are generic issues.

Key messages

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

- Important new technology
- High efficacy rates
- Existing therapies, while effective for many, do not work for *all* those requiring treatment
- NICE criteria for biologic therapy – if applied here – limit access for people who would benefit (not just applicable to this technology)

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Guselkumab for treating moderate to severe plaque psoriasis [ID1075]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	British Society for Rheumatology, [redacted]

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	British Society for Rheumatology exists to promote excellence in the treatment of people with arthritis and musculoskeletal conditions and to support those delivering it. It is a professional association representing the whole multi-disciplinary team: consultant rheumatologists, trainees, specialised nurses, physiotherapists, occupational therapists, psychologists and GPs with special interest in rheumatology. The society aims to improve standards of care in rheumatology and secure a high priority for rheumatology services.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve	

mobility, to cure the condition, or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the	

treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Individuals with accompanying psoriatic arthritis may get additional benefit from guselkumab reflected in quality of life measures and health utility gains should it be effective for psoriatic arthritis as well as skin psoriasis
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	This depends on how QALYs are calculated. There may be improvements in physical function related to improvement in activity of arthritis that are not captured by sole use of dermatology outcome measures.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator	

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

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

-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Guselkumab for treating moderate to severe plaque psoriasis in adults [ID1075]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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About you	
1. Your name	[redacted]
2. Name of organisation	[redacted], British Dermatological Nursing Group
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**x** yes

Thank you for your time.
Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Guselkumab for treating moderate to severe plaque psoriasis [ID1075]

Clinical Expert Questions

1. **Current practice**
   a. Of the NICE-recommended biologic treatment options for moderate to severe psoriasis (adalimumab, etanercept, infliximab, ixekizumab, secukinumab and ustekinumab), which are most commonly used in current NHS practice? Please comment on your experience as well as any registry data that you have access to (for example, the BAD Biologic Interventions Register)

   We have over 750 patients in our clinic on biologic treatments for psoriasis. We have the most patients on adalimumab and ustekinumab. We have smaller cohorts on all the other biologics. I have worked with biologics for over 18 year as an advanced nurse practitioner and a clinical nurse specialist. I co - chair the biologics subgroup of the British Dermatology Nursing Group

   b. Which are considered the most and least clinically effective?
   I would support the evidence presented in British Association of Dermatologsts biologic guidance 2017

   Do they have a similar adverse event profile? (type, frequency & severity)
   I would support the evidence presented in British Association of Dermatologsts biologic guidance 2017

   c. Is ixekizumab widely used in current NHS practice? Can you comment on the reasons for this, and do you expect it to change over time? *I think it will be increasingly used as experience and familiarity grows. There is a cohort of patients for a variety of reasons have failed all other biologics and are desperately waiting for new treatments to be approved by NICE. For biologic naive patients we tend to use the ones we know the most about if no extenuating circumstances*

   d. If psoriasis is unresponsive to one biologic, is it likely to be unresponsive to other biologics? Does this relate to the mechanism of action?

   It depends – some patients respond better to one pathway that another others respond to all and some have very recalcitrant disease. This is why choice of biologics is so very important. We also currently have no methods to determine which biologic will be most safe and efficacious for a patient without trailing it in them.

e. Does psoriasis respond differently to the different types of interleukin inhibitors? That is, does it respond differently to inhibitors of IL-23 (guselkumab), IL-12/23 (ustekinumab) and IL-17 (ixekizumab and secukinumab)?

Please see answer d

f. Are adalimumab biosimilars (Amgevita and Cytlezo) routinely available in current NHS practice in England?
Not in my experience

2. Expected use of guselkumab

a. Guselkumab has a marketing authorisation for moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. This would permit its use as an alternative to phototherapy and non-biologic systemic treatments. Would you expect to use guselkumab as an alternative to, or only after, these treatments?

Unable to comment

b. Where would guselkumab fit into the treatment sequence of biologics for psoriasis?

Unable to comment

3. Safety and efficacy of guselkumab

a. Trial data suggests that guselkumab is superior to other NICE-recommended biologics for psoriasis. Are these benefits observed in real world practice*?*
I have no experience of using gusekumab in the real world

b. Are the benefits of guselkumab clinically meaningful benefits compared with current care? Your answer may differ for different comparator biologic treatment options.
I have no experience of using gusekumab in the real world

c. Does guselkumab have similar adverse events to the NICE-recommended biologic treatments for moderate to severe psoriasis? In particular, how does the tolerability of guselkumab compare with ustekinumab and adalimumab?

I have no experience of using gusekumab in the real world

4. Resource use

a. The company has assumed that guselkumab will have the same resource us as other biologics (excluding infliximab). That is, the company assumes comparable costs associated with drug administration, patient monitoring and follow-up, and management of adverse events. Is this a reasonable assumption? *Yes – it would definitely need this*

5. **Stopping treatment**
    a. Is it reasonable to assume that the long-term probability of discontinuing treatment is the same for all biologic treatments? *Potentially in real work experience. Some of the newer biologics have promising clinical trial data but this is sometimes not reflected in practice.*
    b. In particular, would it be the same for guselkumab, ustekinumab and adalimumab? *I would guesstimate so*
    c. Is it appropriate to assume a 20% discontinuation rate each year for all biologics? *Potentially depending on the criteria used*
    d. What percentage of patients whose disease has responded to treatment might discontinue due to achieving complete freedom of psoriasis? *In my experience all biologics are a treatment not a cure and we have not been able to achieve that – any patient who stops treatmet will find their psoriasis reoccurs*

6. **Induction treatment**
    a. What is the duration of induction treatment with guselkumab and when is the first maintenance dose administered? *100mg sc administered at week 0 and week 4 and then every 8 weeks*
    b. How is the duration of induction treatment with a biologic defined? *When the loading doses are administered – in this care at week 0 and week 4*.
    c. Does it consider the half-life of the drug? *Not qualified to answer this!*

NICE National Institute for Health and Care Excellence

Clinical expert statement

Guselkumab for treating moderate to severe plaque psoriasis in adults [ID1075]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- 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.

About you	
1. Your name	[redacted]
2. Name of organisation	[redacted]
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with this condition? x☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	x☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	

7. What is the main aim of treatment?	To treat patients with moderate to severe psoriasis effectively – i.e. improving the signs and symptoms of psoriasis.
8. What do you consider a clinically significant treatment response?	This has been pre-defined by NICE as an improvement in the psoriasis area and severity index of 75 % (PASI 75) or a PASI 50 with a 5 point drop in DLQI. This definition is reasonable in my opinion and correlates with a clinically meaningful improvement.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, although we have had a number of new therapies for this population in recent years there is a 15% per annum loss of response even with the better performing biologics such that sequential use of therapies is a reasonable strategy to give medium to long term control of what is a life-long disorder.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	When patients with moderate to severe psoriasis (i.e. PASI > 10 and DLQI >10) have tried and failed or are unsuitable to use methotrexate, ciclosporin and phototherapy they can move onto a biologic.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Yes, it is well defined. There is debate around using biologics in those with high impact disease who may have a PASI < 10 – for example facial of genital involvement. That said, the approach is well standardised.

state if your experience is from outside England.)	
• Of the NICE-recommended biologic treatment options for moderate to severe psoriasis (adalimumab, etanercept, infliximab, ixekizumab, secukinumab and ustekinumab), which are most commonly used in current NHS practice? Please comment on your experience as well as any registry data that you have access to (for example, the BAD Biologic Interventions Register)	Ustekinumab and adalimumab are the most commonly used with the first of the Il17's launched (secukinumab) being used 3rd most frequently used. Ustekinumab is used more in the setting where patients have psoriasis alone and in the case of adalimumab when a patient has concomitant psoriatic arthritis. I am part of the BAD biologics registry steering committee and research committee so the above is a reflection beyond my own clinical practice and reflects BAD Biologic Interventions Register data. It should also be noted that the use of the drugs is also in part related to their longevity of access i.e. use of ixekizumab is more modest due to its recent launch.
• Of the NICE-recommended biologic biologics, which are considered the most and least clinically effective?	Ustekinumab is recommend 1st line in the latest BAD biologics guidelines based on: Longer term persistence data versus adalimumab (from the BAD Registry. 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).

	Warren RB, Smith CH, Yiu ZZN, Ashcroft DM, Barker JNWN, Burden AD, Lunt M, McElhone K, Ormerod AD, Owen CM, Reynolds NJ, Griffiths CEM. J Invest Dermatol. 2015 Nov;135(11):2632-2640. Adalimumab is still the favoured drug in the setting of concomitant psoriatic arthritis. However, this guideline could not assess longer term (registry) data on the IL17s as none were available. All available IL17's have been shown to be more effective (in clinical trials) than ustekinumab BUT of course longer term real world safety is not established. Etanercept is the least effective and its use has dramatically declined in the last 5 years with very few new initiations. Infliximab is also rarely used based on worse safety profile and poor persistence on the drug due to high levels of immunogenicity.
• What impact would guselkumab have on the current pathway of care? Where would guselkumab fit into the treatment sequence of biologics for psoriasis?	Guselkumab is highly effective drug as shown by the clinical trial program. It is statistically superior to adalimumab and also works in patients better than ustekinumab (note odd trial design, but outcome not in doubt). As mentioned above of the current biologics ustekinumab is the most persistent and this in part is because of its dosing schedule (every 12 weeks). An infrequent dosing schedule leads to better adherence and allows nurses to actually ensure the patient is given the drug. Thus, it is likely that Guselkumab, being dosed every 8 weeks , will also show this same beneficial persistence in the medium to long term that ustekinumab does. Given it is highly effective in clinical trials AND has the inherent advantage of infrequent dosing versus Il17s and adalimumab it is likely, that once is safety is established in the real world, it will be used early in the biologics treatment pathway.
11. Do you expect the technology to provide clinically	Yes for the reasons given above i.e more people with this life-long condition gaining stable longer lasting control I believe this benefit will be borne out versus all existing drugs (including Il17s) in the medium to long-term.

meaningful benefits compared with current care? Or are the health benefits likely to be similar? Your answer may differ for different comparator biologic treatment options.	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The population is well defined and suitable. i.e. moderate to severe chronic plaque psoriasis.
The use of the technology	
13. Will the technology be used in the same way as current care in NHS clinical practice?	yes
• In what clinical setting should the technology be used? (For example,	Secondary and tertiary care

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	By and large infrastructure exists to allow implementation of this treatment
14. How does healthcare resource use differ between guselkumab and current biologic treatment options? Will guselkumab be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	No, its use will be very similar to existing biologics so no additional / different resource required.

or ease of use or additional tests or monitoring needed.)	
• The company has assumed that guselkumab will have the same resource us as other biologics (excluding infliximab). That is, the company assumes comparable costs associated with drug administration, patient monitoring and follow-up, and management of adverse events (note that the company provide a homecare service for administering the drug, meaning the NHS does not incur administration costs). Is this a reasonable assumption?	yes

15. Will any rules (informal or formal) be used to start or stop treatment with the technology?	They are in place already as per prior HTAs and NICE psoriasis care guidelines CG 153
• What are these rules usually based on?	For initial response to the drug the time point used in the clinical trial as a primary end point (week 16) will be used to assess PASI And DLQI improvement. These parameters should then be assessed at future visits (3 monthly for 2 years) and then 6 monthly thereafter to show continued response of at least PASI 75 OR PASI 50 and 5 point drop in DLQI.
• After how long would you expect to assess response to treatment with guselkumab, to inform the decision on whether to continue treatment?	See above
• Do starting and stopping rules include any additional testing?	Yes, see above
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes for reasons of both high initial response and likelihood of high ongoing persistence

impact on health-related benefits and how might it improve the way that current need is met?	
17. How do any side effects of the technology affect the management of the condition and the patient's quality of life?	From the clinical trial data AEs are very low and there was nil surprising. By and Large biologics are tolerated exceptionally well by patients and considerably better than most systemics. Of course mandating sign up to BADBIR would be helpful to ensure accurate collection of longer-term safety data.
• Does guselkumab have similar adverse events to the NICE-recommended biologic treatments for moderate to severe psoriasis? In particular, how does the tolerability of guselkumab compare with ustekinumab and adalimumab?	Yes, if anything some suggestion from the clinical trials of even lower event rates vs. ustekinumab and adalimumab .
• Based on your experience, do the NICE-	Infliximab higher

recommended biologic treatment options for moderate to severe psoriasis have similar adverse events? (type, frequency & severity)	Others similar For example see Risk of Serious Infection in Patients with Psoriasis on Biologic Therapies: a Prospective Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). Yiu ZZN, Smith CH, Ashcroft DM, Lunt M, Walton S, Murphy R, Reynolds NJ, Ormerod AD, Griffiths CEM, Warren RB; BADBIR Study Group. J Invest Dermatol. 2017 Oct 17.
Sources of evidence	
18. Do the clinical trials on guselkumab reflect current UK clinical practice?	To a large extent given how this HTA is being performed Very useful to have a H2H study versus adalimumab.
• 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?	PASI / DLQI given how we currently assess response to biologics in the UK and both key end points in the study
• Are there any adverse effects that were not	Nil to my knowledge

apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for adalimumab and ustekinumab since the publication of NICE technology appraisal guidance for these treatments (TA146 and TA180)?	Given above in ref form from the registries.
21. How do data on real-world experience compare with the trial data?	Generally the drugs don't do as well in the real world. See data given above. Ustekinumab (probably because of adherence to drug mimics trails most closely in longer-term)

	This is why in my opinion guselkumab with its dosing advantage becomes an important drug for the coming years.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not to my knowledge
22b. Consider whether these issues are different from issues with current care and why.	n/a
Other topic-specific questions	
23. Is it reasonable to assume that the probability of discontinuing treatment is the same for all biologic treatments?	No see ref above on persistence
• In particular, would it be the same for	No and reasons for this given above

guselkumab, ustekinumab and adalimumab?	
• Is it appropriate to assume a 20% discontinuation rate each year for all biologics?	See data above
What percentage of patients whose disease has responded to treatment might discontinue due to achieving complete freedom of psoriasis?	Very few. Most who clear stay on drug even when clear
24. Does psoriasis respond differently to the different types of interleukin inhibitors? That is, does it respond differently to inhibitors of IL-23 (guselkumab), IL-12/23 (ustekinumab) and IL-17 (ixekizumab and secukinumab)?	Yes, the reasons for this are unclear but being investigated by the PSORT consortium www.psort.org.uk One key one mentioned already is around adherence

25. If psoriasis is unresponsive to one biologic, is it likely to be unresponsive to other biologics? Does this relate to the mechanism of action?	There is evidence that if you fail one biologic then you are at higher risk of failing subsequent ones; however many people fail 1,2 or more and then do go on to find a biologic that is effective and works for them for a sustained period. Although some of the mechanisms of action are similar (e.g. adalimumab and infliximab) it is not always the MOA that predicts sequential failure – more likely other properties (immunogenicity / adverse events varying between drugs of same class) of the drugs that vary.
26. Are adalimumab biosimilars (Amgevita and Cytlezo) routinely available in current NHS practice in England?	No , not yet
27. How is the duration of induction treatment with a biologic defined? Does it consider the half-life of the drug?	Induction is usually over 12- 16 weeks but does vary depending on the therapy
• Is the first maintenance dose given immediately after completing induction or might there be a delay?	The dosing will be weeks 0,4 then 8 weekly thereafter with no expected delay after completing induction.

• What is the expected duration of induction treatment with guselkumab?	As above

Key messages

28. In up to 5 bullet points, please summarise the key messages of your statement.

- Guselkumab is a highly effective drug in clinical trials for patients with moderate to severe psoriasis
- Guselkumab is more effective in trials than adalimumab
- Given the dosing schedule of every 8 weeks and experiences to date with ustekinumab it can be expected that Guselkumab will prove over time to not only be a highly effective short-term drug but also medium to long-term drug and (in my opinion) out perform all existing biologics in the long –term (individual opinion, no evidence at this stage).
- Adherence is likely to be good as 8 weekly dosing will potentially allow nurse administration
- Safety event rates were low in the clinical trials with no unexpected signals.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Evidence Review Group's Report

Title: Guselkumab for treating moderate to severe plaque psoriasis

Produced by	*Warwick Evidence*
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Date completed	*22/01/2018*

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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.

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Contributions of authors

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

Glossary of terms

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

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

The technology is not pharmacologically similar to the comparators

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

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

The selected comparators are appropriate

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

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

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

Strength of the case for undertaking an FTA

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

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

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

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

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

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

3.1 The submission

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

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

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

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

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

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

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

3.2 ERG's critique of clinical effectiveness evidence submitted

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

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

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

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

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

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

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

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

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

3.3 ERG's critique of safety evidence submitted

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

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

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

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

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

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

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

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

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

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

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

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

4.1 Company cost comparison

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

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

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

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

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

Previous assessments of the biologics

Table 1: Timing of previous STAs and NICE recommendations

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

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

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

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

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

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

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

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

Market share and comparators

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

[redacted]

[redacted]

[redacted]

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

[redacted]

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

[redacted]

Since the company has already included adalimumab in the cost comparison there seems little harm in the cost comparison encompassing all the subcutaneous biologics approved by NICE[3], though both [redacted]. Ixekizumab may be of [redacted] but may be relevant from a cost effectiveness viewpoint since it was approved after secukinumab so might help indicate what could happen if guselkumab was judged unsuitable for an FTA and was sent down the STA route.

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

Cost comparison: Clinical effectiveness

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

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

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

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

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

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

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

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

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

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

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

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

Considerations if guselkumab were to proceed to an STA

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

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

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

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

[5] Table 114

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

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

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

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

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

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

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

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

Drug cost calculations: CS Table 22 Document B

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

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

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

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

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

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

Drug cost calculations: Cost comparison assuming clinical similarity

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

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

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

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

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

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

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

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

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

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

Drug cost calculations: Cost comparison differentiating clinical similarity

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

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

Sensitivity analyses are also presented:

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

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

Table 7: Cost comparison with subcutaneous biologics: total costs

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

Table 8: Cost comparison with subcutaneous biologics: net costs

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

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

[redacted]

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

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

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

4.2 Conclusions

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

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

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

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

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

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

[redacted]

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

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

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

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

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

Recommendations

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

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

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

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Appendix 1: Errata in company submission

The ERG have identified the following errors within the CS.

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

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

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

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

4. Additional errors identified in Tables:

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

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

Appendix 2: Discontinuation studies

Summary

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

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

These papers do not cover secukinumab, ixekizumab or guselkumab.

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

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

Individual papers

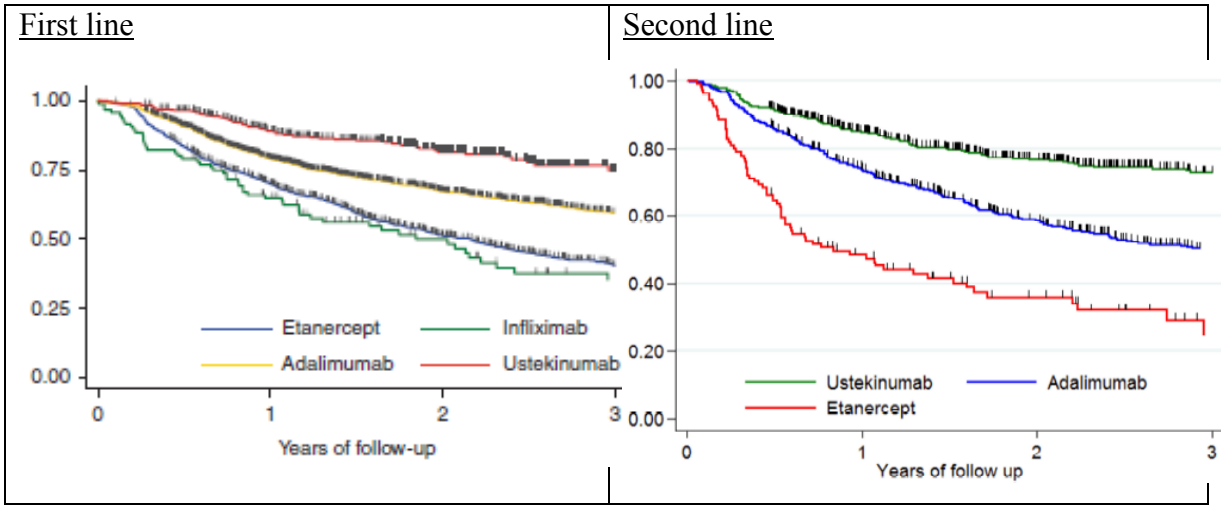
Warren et al (2015)[13] analysed the prospective cohort study data from the British Association of Dermatologists Biologic Interventions Register (BADBIR). This focussed upon the 3,523 biologic naïve patients receiving a first course of a biologic with data for infliximab (n=96), adalimumab (n=1,879),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

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

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

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

Table 01: Discontinuation reported by Warren and Iskander



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

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

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

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

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

Updated response to NICE Jan 2018

Background

In its scrutiny meeting of 19 December in which NICE discussed the appropriateness of the topic continuing as a Fast Track Appraisal, it was felt that guselkumab is likely to provide greater benefit at greater cost to the healthcare system. This is based upon the ERG's assessment that a greater number of patients are likely to continue on guselkumab after 16 week induction due to its better efficacy than would be the case with adalimumab and / or ustekinumab (lower efficacy). In response to this, Janssen argued that guselkumab offers superior value to the NHS by offering greater benefits at [redacted] in induction phase, and a) [redacted] in maintenance versus adalimumab, and b) greater benefits at [redacted] when compared to the market leader, ustekinumab.

In our submission to NICE, we presented a simple cost comparison scenario where patients received no further treatment for psoriasis once they discontinue a biologic treatment. This scenario was built to enable a simple cost comparison without considering the differences in efficacy and discontinuation rates based purely on annual treatment costs (see Table 1).

Table 1: Annual expected costs excluding discontinuation

Therapy	Annual expected cost (including induction)	Annual expected cost per subsequent year	Total expected cost over 5 years
Adalimumab	£9,684	£9,156	£46,306
Ustekinumab	£10,735	£9,304	£47,950
Guselkumab	[redacted]	[redacted]	[redacted]

However, this scenario may not reflect current UK clinical practice where biologics are used sequentially, and thus patients may receive 3 or more biologic therapy lines. To model clinical practice in the UK, we have updated our cost-comparison model to incorporate up to 2 subsequent therapy lines. In this updated analysis, a second therapy line comprising either adalimumab or ustekinumab was used and a third therapy line (which is modifiable in the model) includes the cost of another biologic such as Infliximab. As required by NICE, we have modelled the costs based upon PASI 75 response rates, with a 20% discontinuation rate applied to all biologics.

The results of this updated cost-comparison analysis demonstrate that over a five-year time horizon, guselkumab [redacted] when compared to adalimumab and ustekinumab. To pressure test the assumptions in the base case and to gauge the impact on overall cost of using guselkumab, a scenario analysis was also performed. The result of the scenario analysis was consistent with the base case results and further confirmed that guselkumab [redacted] alternative compared to adalimumab and ustekinumab.

In conclusion, based upon the revised and more rigorous analysis, Janssen is confident that guselkumab offers excellent value for to the NHS and offers greater benefits at similar or lower cost to NICE approved biologics in current clinical practice and therefore meets the criteria to continue as a Fast Track Technology Appraisal (FTA).

New base case analysis

Key assumptions

For the new base case, it was assumed that once patients discontinue guselkumab, they will switch to adalimumab or ustekinumab in equal proportions i.e. 50:50. This assumption is based upon [redacted]. Based on this assumption, patients that discontinue adalimumab will switch to ustekinumab, and patients that discontinue ustekinumab will switch to adalimumab. Consistent with previous NICE TAs (TA350, TA442), infliximab was chosen as the third therapy line. For the purposes of this analysis, the cost of the cheapest infliximab biosimilar, Flixabi, was used (£10,226).

Sequences used:

1) Sequence 1: **Guselkumab** > adalimumab (50%) / ustekinumab (50%) > infliximab
2) Sequence 2: **Adalimumab** > ustekinumab > infliximab
3) Sequence 3: **Ustekinumab** > adalimumab > infliximab

New base Case results

The results of the new base case are presented in Table 2. The result of the new base case analysis shows that over a five year time horizon, guselkumab [redacted] compared to adalimumab ([redacted] per patient) and ustekinumab (a [redacted] per patient).

Table 2 - New base case

Therapy	1st line	2nd line	3rd line	Total 5 years	Diff vs GUS
Drug	**First line**	**Second line**	**Subsequent**	**Total drug cost per 5 years**	**Cost difference**
Guselkumab	[redacted]	[redacted]	[redacted]	[redacted]	
Adalimumab	£19,811	£15,942	£14,240	£49,994	[redacted]
Ustekinumab	£24,477	£11,681	£14,240	£50,398	[redacted]

Scenario Analysis

To pressure test the assumptions in the base case presented above, five different scenarios were modelled as described below. The results of this analysis are presented in Table 3 over page.

1. All guselkumab patients switch to adalimumab after discontinuation
2. All guselkumab patients switch to ustekinumab after discontinuation
3. Ustekinumab 45mg PASI 75 efficacy (63%) is used instead of 90 mg efficacy (71%)
4. Lower cost of infliximab biosimilar equal to its maintenance cost of £8,577
5. Using different discontinuation rates i.e. 20% ADA, 8% UST, 8% GUS

Table 3 – Scenario analyses

Scenario	1st line	2nd line	3rd line	Total cost 5 years	Diff vs ADA	Diff vs UST
1	[redacted]	£10,398	£12,006	[redacted]	[redacted]	[redacted]
2	[redacted]	£13,013	£10,523	[redacted]	[redacted]	[redacted]
3	[redacted]	£11,343	£11,640	[redacted]	[redacted]	[redacted]
4	[redacted]	£11,706	£9,448	[redacted]	[redacted]	[redacted]
5	[redacted]	£8,153	£6,515	[redacted]	[redacted]	[redacted]

The results of the scenario analyses (1-5) are consistent with the new base case results and further confirm that guselkumab is a [redacted] alternative compared to adalimumab and ustekinumab when used as a first line biologic.

- In scenario 1, where all guselkumab patients switch to adalimumab after discontinuation, [redacted] driven by the lower efficacy of adalimumab, leading to [redacted]
- In scenario 2, where all guselkumab discontinuation patients switch to ustekinumab, guselkumab [redacted]. Although the [redacted] than in the new base case, this can be explained by the higher efficacy of ustekinumab (71%) vs. adalimumab (61%).
- TA 350 and TA 442 used the efficacy of ustekinumab 90mg in the cost effectives analysis and for that reason it was selected for the new base case analysis. In scenario 3, the efficacy of the 45mg dose is used (63%). In this case, guselkumab [redacted]
- In scenario 4, where the cost of infliximab biosimilar is used in maintenance (£8,577), instead of the induction year cost (£10,226), guselkumab [redacted].
- Lastly, scenario 5 models a scenario where differential discontinuation rates are used. Guselkumab and ustekinumab were assumed to have a similar discontinuation rate, i.e. 8%, while adalimumab discontinuation rates were maintained at 20%. Even in this scenario, guselkumab is [redacted]

In summary, all scenario analyses support our assertion that guselkumab is a cost-effective option compared to adalimumab and ustekinumab.

Revised company submission

The company submits an analysis of sequences of 3 treatments over a 5 year time horizon. These apply the company NMA treatment specific PASI75 estimates and assume a common 20% annual discontinuation rate among responders on maintenance therapy thereafter.

	1st line	2nd line	3rd line	Total	net
guselkumab	guselkumab [redacted]	50:50 adal:uste £11,706	infliximab £11,265	£49,407	..
adalimumab	adalimumab £19,811	ustekinumab £15,942	infliximab £14,240	£49,994	[redacted]
ustekinumab	ustekinumab £24,477	adalimumab £11,681	infliximab £14,240	£50,398	[redacted]

Revised model cross check

The company has submitted a revised model which costs sequences of 3 treatments. It is somewhat more involved than the original model. The ERG does not yet understand some of the structures of the revised model. The ERG has not rebuilt or cross checked the revised model in any way, other than casting a cursory eye over the various sheets. As a consequence, the ERG cannot comment upon the correctness of the revised model estimates.

Revised model time horizon

As per the ERG report for the DMF assessment [TA475], while a 10 year time horizon is largely sufficient for a comparison of single treatments given a 20% annual discontinuation rate, it is insufficient for a comparison of sequences of 3 treatments. A 5 year time horizon is far too short.

Comparators and sequencing

Within a cost comparison of single treatments the original ERG scrutiny report argued for consideration of secukinumab. It also argued for consideration of ixekizumab to assess where an STA might head if guselkumab was judged unsuitable for an STA. Ixekizumab is the last subcutaneous biologic approved by NICE and has a similar PASI75 response estimate to that of guselkumab, meaning that an STA would probably be able to concentrate upon the differences in the [redacted] costs between guselkumab and ixekizumab.

Within modelling of sequences of 3 treatments it seems even less reasonable to ignore the other subcutaneous biologics. These will be used within treatment sequences.

Guselkumab is being assessed for use among the moderate to severe. NICE has only approved infliximab for the very severe.

The ERG is sceptical of the assumption that the 3rd line treatment will be infliximab.

The revised company submission assumes that all patients who cease 2nd line treatment receive 3rd line infliximab.

- The annual 1st year costs of infliximab are estimated to be £10,226, and the annual maintenance costs are estimated to be £8,577.
- As far as the ERG can ascertain:
  - Infliximab is not associated with a PASI75 response estimate and does not have the 20% annual discontinuation rate applied. All patients who receive infliximab remain on it and incur its costs indefinitely[1].
  - The company does not apply the £8,577 annual maintenance cost of infliximab but rather assumes that all years incur the higher £10,226 1st year cost[2].

Assuming that all patients who receive infliximab remain on it thereafter is untenable. A worse PASI75 for 1st line treatments causes patients to incur infliximab costs earlier and so for a longer duration. This biases the analysis against adalimumab and ustekinumab and in favour of guselkumab.

In the light of the above, the ERG thinks that it is more reasonable to exclude the infliximab costs from the revised company modelling[3]. Given the company model structure, this means that only sequences of two treatments are considered. In effect it is assumed that after 2nd line the costs incurred will be similar between sequences. Over a 5 year time horizon the guselkumab sequence is [redacted] than the adalimumab sequence by [redacted] and is [redacted] than the ustekinumab sequence by [redacted], while over a 10 year time horizon the [redacted] in cost are [redacted] and [redacted] respectively.

[1] The company model has not been written up in the 2nd company submission, but the electronic copy notes that "*Expected time post second line is calculated as time horizon less sum of time on first and second line therapies*".
[2] Setting the £8,577 to £0 in cell C28 of *Drug Costs* has no effect upon results. Similarly, setting the £10,266 to £0 in cell C27 of *Drug Costs* causes the 3rd line treatment costs to fall to £0.
[3] Implemented by setting cells C27 and C28 of *Drug Costs* to zero.

Alternative approach

Since there has not been time to parse the company model, and in line with the company drug costings not incorporating discounting or mortality as per cost consequence FTA guidance, a more transparent mathematical approach can be adopted.

An annual discontinuation rate of 20% implies that the mean post induction duration of treatment is 5 years. For a treatment with an induction cost of £X, a PASI75 response rate of Z% and an annual maintenance cost of £Y this implies a total undiscounted cost of:

- £X + Z%*£Y*5

This can be used to calculate the total costs of each line of treatment in a sequence of treatments.

This, as with the company cost consequence modelling, requires that assumptions be made about treatments' PASI75 rates at 2nd line and at 3rd line. The usual approach, and the approach adopted by the company in its modelling of treatment sequences, is to assume the same PASI75 effectiveness at 2nd line and 3rd line as at 1st line.

If this approach is adopted it is immediately obvious that the cost of treatment A followed by treatment B is exactly the same as the cost of treatment B followed by treatment A, regardless of their relative clinical effectiveness. The ordering of treatments does not affect total costs within the cost consequence FTA methodology.

Similarly, if treatment A is followed by treatments C and D and treatment B is similarly followed by treatments C and D, the costs of treatments C and D are common to both sequences. The difference in the costs of the sequences is simply the difference in the costs of the 1st line treatments. Consideration of sequencing adds nothing to the analysis.

Conclusions

The ERG has not cross checked any of the revised company model structure or its estimates.

The company estimates that when sequences of 3 treatments are considered over a 5 year time horizon, the sequence with guselkumab 1st line is [redacted] than the sequence with adalimumab 1st line, and [redacted] than the sequence with ustekinumab 1st line. These estimates apply the treatment specific PASI75 response estimates of the company NMA

If sequences of 3 treatments need to be considered, this would seem to argue for a greater consideration of the subcutaneous biologics.

Guselkumab is being assessed for the moderate to severe. NICE has only approved infliximab for the very severe. The assumption of 3rd line infliximab is questionable.

3rd line infliximab is not associated with any PASI75 estimate or annual discontinuation rate. The revised company model assumes that patients who initiate infliximab remain on it indefinitely. This is untenable and biases results in favour of guselkumab.

The revised company model also appears to apply the higher 1st year induction costs of infliximab to all years. This further biases results in favour of guselkumab.

Removing 3rd line infliximab from the revised company model so that it only considers sequences of 2 treatments and applying a 10 year time horizon results in the sequence with guselkumab 1st line being [redacted] costly than the sequence with adalimumab 1st line, and [redacted] costly than the sequence with ustekinumab 1st line.

In the opinion of the ERG the company consideration of sequences adds little to nothing. For the cost consequence FTA decision, it seems sufficient to concentrate upon the costings of the original company submission, the ERG report based upon this and in particular its cPAS appendix.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Guselkumab for treating moderate to severe plaque psoriasis [ID1075]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 23 January 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Misinterpretation of pivotal trials (VOYAGE 1 and VOYAGE 2)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG have misunderstood the two pivotal trials for guselkumab and have called into question its independence. Page 25-26 *"Third, 43 centres were common to both VOYAGE 1 (101 centres overall) and, VOYAGE 2 (115 centres overall) (see CS; Supplementary Clarification Document). This questions the independence of these studies, as assumed when performing an NMA. This is a problem that may not be unique to guselkumab and the VOYAGE trials, but may also affect other treatments and their relevant trials included in the NMA. In mitigation, NMAs could have been conducted with just one VOYAGE trial included (with sensitivity analyses using the alternative VOYAGE trial). The ERG would anticipate that this*	We kindly request removal of this paragraph	Janssen strongly refutes the ERGs conclusion that Voyage 1 and 2 studies are not independent, based on the following facts: 1. Voyage 1 and 2 have different clinical trial numbers, NCT02207231, NCT02207244 and enrolled different patients. 2. Overall, a majority of centres (between 57%-63%) across the two trials were different. 3. Both are double blinded trials and therefore the investigator bias is limited. 4. And most importantly, these studies have different trial designs. VOYAGE 1 is a head to head study versus adalimumab, while VOYAGE 2 includes a randomized treatment withdrawal and re-treatment period and aims to evaluate the maintenance of response to guselkumab in subjects continuing on a 100 mg q8w regimen compared with the maintenance of response in	It is difficult to identify the factual error that Jansen suggest. The ERG did not "conclude" that the trials were "not independent". Rather, the ERG suggested that common centres (and presumably physicians) for concurrent trials might compromise the independence. Elsewhere, the ERG state that the trials were well conducted. See ERG report Page 9, in the critique of the submitted clinical evidence.

procedure would widen the credible intervals obtained for the comparisons of guselkumab versus other therapies, but not affect the findings."		subjects who have active treatment withdrawn. Overall, having common trial centres does not constitute lack of independence. It highlights the challenge that industry faces in finding trial centres that have the right experience and expertise to run pivotal trials.	

Issue 2 Methodological limitations of the cost comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
A cost comparison using differential efficacy, which assumes no subsequent cost, disadvantages more efficacious therapies. Page 22 - 24	We kindly request removal of these analyses (including Table 7 and Table 8) from the ERG report.	In Janssen's view, the ERG has overcomplicated its analysis by proposing a differential efficacy analysis (budget impact) rather than a simple cost comparison as discussed and agreed at the decision problem meeting. Results presented in Tables 7 and 8 of ERG report, do not represent UK clinical practice and as explained below, are biased against more efficacious therapies like guselkumab and favours treatments with lower efficacy. This effect is further exacerbated when a longer time horizon is used. ERG analysis assumes that patients that discontinue treatment (i.e. primary non-responders) have a zero-subsequent cost and this would mean that patients will not receive any further treatment. This assumption would be appropriate if similar efficacy and similar discontinuation rates were to be assumed (as presented in the CS) as patients would stay on treatment for the same duration. However, when differential efficacy is assumed, it is unrealistic to	Not a factual inaccuracy by the ERG, no change made.

		assume zero subsequent cost. This assumption favours the least efficacious treatment as the patients stay on the treatment for a shorter duration and then these patients cost zero. Under this assumption, more efficacious therapies will always be at a disadvantage and would be forced to price at a discount to less efficacious therapies in order to keep the overall cost comparable. In Janssen's view, this approach only serves to disadvantage guselkumab on account of its better efficacy, we therefore suggest that the ERG should either remove this analyses or include the cost of non-responders (i.e. cost of subsequent treatment) in their analyses to provide a more balanced view of the associated costs. Notwithstanding the above, Janssen submitted a supplementary analysis on 5 January 2018 as requested by NICE technical team, that simulated the cost consequence of using subsequent therapy lines. However, the ERG in their rebuttal of this supplementary analyses presented its own analyses, which noted "*In effect it is assumed that after 2nd line the costs incurred will be similar between sequences".* Once again, the ERG has	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		assumed a zero cost for non-responder after a patient has received two lines of treatment. This assumption suffers from the same previous limitations which makes it clinically implausible as there will be a subsequent therapy cost and methodologically incorrect as it disadvantages more efficacious therapies. We firmly believe that for the purposes of this appraisal, a cost comparison assuming similar efficacy (as presented in the company submission), is a more appropriate methodology, which is simple, pragmatic and in-line with the FTA process.	

Issue 3 The choice of comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
There is inconsistency in ERG's view of the appropriate comparator across the report. ERG agrees with the choice of comparators in some parts and in other places either doubts the validity of the comparator or suggests additional comparators. Page 4 "*The selected comparators are appropriate" […] "Overall, the ERG agrees that the comparator treatments used in the company submission (CS) meet the criteria set by NICE"* [redacted] *".* Page 25 "*If it applies ustekinumab should not be a comparator."*	We kindly request removal of this factually inaccurate statements about comparators from the document. Please remove the following [redacted] and "*If it applies ustekinumab should not be a comparator."*	At the Decision Problem Meeting, it was agreed with the NICE technical team and the ERG that the company will only present a simple cost comparison vs. most appropriate comparator. The choice of comparator has been extensively justified within the company submission and is based on current market share and the therapy that guselkumab is most likely to displace in UK clinical practice. Based on historical evidence, guselkumab is more likely to displace less efficacious and older therapies such as adalimumab and ustekinumab and less likely to displace newer agents such as in IL-17 class (secukinumab and ixekizumab), which represent a growing but a smaller share of the market ([redacted]). Both secukinumab and ixekizumab have a confidential PAS whereas adalimumab and ustekinumab have no confidential pricing arrangements. This enables an unbiased cost comparison. The most recent data from the DERMBIO Registry, as noted in ERG report, show that secukinumab has one of the highest discontinuation rates of any new biologics and therefore, the long term efficacy of secukinumab in real world is uncertain. These results when seen alongside with safety signals noted with the IL-17 class, namely IBD exacerbation, candida infections and other AEs, could potentially (negatively) impact future uptake and use of IL-17 agents in UK clinical practice. More importantly, a positive guselkumab NICE recommendation post FTA, would inevitably contain a statement to the effect that *the least expensive agent should be chosen* in clinical practice. In view of these points the ERG's consideration of other comparators is an unnecessary overcomplication.	The ERG's position is that there are multiple potential comparators. All the ERG statements about possible comparators were conditional upon the criteria for selection to be applied e.g. effectiveness, cost, market share etc.

			In addition, real world discount rate for ustekinumab is not relevant to the company model (20% discount applied for all drugs). No change made.
Page 25 *ERG recommends that secukinumab should be a comparator because of its rising market share.*	This statement is factually inaccurate and we kindly request this sentence to be removed	Janssen disagrees with the ERG assumption that guselkumab will take market share from secukinumab. Based on historical evidence, new product introductions primarily take market share from older and less efficacious agents with sizable market shares rather than similarly efficacious and recently introduced products with lower market shares. There are numerous examples of this across different therapy areas including in psoriasis, as noted in the ERG report. When reviewing the evolution of market shares in psoriasis market over time (see Table 2 in the ERG report), one observes that: 1. the [redacted] in market share of secukinumab is associated with a corresponding [redacted] in market share of etanercept (TA103 July 2006) and adalimumab (TA146 June 2008); and 2. market share of ustekinumab (TA180 September 2009) has stayed relatively stable.	This is not a factual error. This is opinion/interpretation about a fact submitted by Jansen (market share of secukinumab and ustekinumab). No

		This leads us to conclude that [redacted], which was the more recent introduction at the time of secukinumab launch, albeit six years apart. This would suggest that guselkumab [redacted] to take market share from adalimumab and ustekinumab and [redacted] from secukinumab as suggested by the ERG. Similarly, ERG's assertion that ixekizumab should be considered as a comparator as it would lose its market share to guselkumab, is not supported by past trends.	change made
ERG have made statements about market share calls that are not supported by past trends. Page 15 "*Adalimumab has a [redacted] market share so seems [redacted]*."	Suggested amendment: *Adalimumab has a [redacted] market share so seems [redacted]*	As noted in the ERG report, adalimumab [redacted] while secukinumab [redacted] in terms of the market share. With ustekinumab [redacted] in terms of the market share, it is only logical to conclude that [redacted] (refer to previous comment). [redacted] (please see Table 2 in the ERG report). This provides further credence to our argument that [redacted]	The ERG comments /statements are not factual errors. These are interpretations based on estimates that are recognised to be associated with appreciable uncertainties. No change made

ERG have included information that is not public knowledge or NICE stated position. Page 25 "*NICE briefings have indicated that any comparator for an FTA should not be the most expensive or the least effective. This is not mentioned in the FTA guidance notes and the ERG is consequently unclear of its status. If it applies ustekinumab should not be a comparator.* *The FTA guidance notes also do not specify that the comparator cannot be a treatment that is marketed by the company. Janssen markets ustekinumab. The ERG is unclear whether there are any concerns if the company can only demonstrate lower drug costs against a comparator it also markets and prices."*	We kindly request removal of these two paragraphs.	The FTA guidance does not explicitly state that the most expensive and the least effective therapy be excluded as a comparator. Additionally, it is unclear that ustekinumab has the highest cost of all the subcutaneous therapies based on the analysis shown in Table 4 of the ERG report. Lastly, the fact that Janssen does manufacture and market ustekinumab is irrelevant to its appropriateness as a comparator. Ustekinumab was chosen as a comparator based on its market leadership position, transparent pricing (no confidential PAS) and the likelihood of it getting displaced by guselkumab.	The comment on page 25 is a point of clarification regarding the process, not a statement of fact. This is a point that has been discussed at various meetings with NICE during the FTA process. This is not a factual inaccuracy by the ERG, however we have changed the paragraph to AIC.

			Regarding the comment that *'Janssen markets ustekinumab'*, this is not a factual inaccuracy by the ERG, no change made.

Issue 4 Misinterpretations related to NMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
1. On page 9 of the ERG report, the incorrect figures are being referenced from the CS documents when describing "…a series of 'full' NMAs which compared guselkumab to all possible systemic biological psoriasis treatments, including treatments not licensed for treating plaque psoriasis in the	We kindly request that the referenced figures: (CS; Figures 19 – 27, Document B Appendix D) for the full evidence network NMAs be changed to (CS; Figures 19-39, Document B Appendix D).	The analyses currently being referenced are the unadjusted full evidence network NMAs. Changing the referencing to the proposed amendment would reference all unadjusted and adjusted NMAs for the full evidence network.	ERG agree and will change reference to: (CS; Figures 19-39, Document B Appendix D)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
UK (CS; Figures 19 – 27, Document B Appendix D)".			
2. On page 9 of the ERG report, the incorrect figures are being referenced from the CS documents when describing "…additionally performed sensitivity analyses restricting the NMAs to only comparators specified in the decision problem (CS; Figures 28 – 36, Document B Appendix D)".	We kindly request that the referenced figures: (CS; Figures 28 – 36, Document B Appendix D) for the sensitivity analyses for the restricted NMAs specified in the decision problem be changed to (CS; Table 8 and Figures 11-29, Clarification Document).	The analyses currently being referenced as sensitivity analyses for the restricted network are those from the baseline-risk adjusted NMAs, based on the full evidence network. Changing the referencing to the proposed amendment would accurately reference the sensitivity analyses for the restricted network NMAs.	ERG agree and will change reference to: (CS; Table 8 and Figures 11-29, Clarification Document)
3. On page 10 of the ERG report, the following is stated: "…however it is unclear if these findings are based on the unadjusted or placebo-adjusted model."	We kindly request this sentence be removed.	The analysis is based on an unadjusted NMA. For continuous outcomes, such as a mean change in DLQI, baseline-risk adjusted (i.e., placebo-adjusted) models cannot be performed.	ERG would kindly request all analyses are accurately described and labelled to avoid potential misunderstanding. With this additional information, ERG agrees to remove this sentence.
4. On page 10 of the ERG report, the incorrect table is being referenced when describing "…the company presents a number of adjusted NMAs (CS; Table 12, Document B)"	We kindly request that the referenced table: (CS; Table 12, Document B) be changed to (CS; Table 12-13, Document B Appendix D).	The table currently being referenced is "Physician- and patient-reported outcomes in VOYAGE 2 at Weeks 16 and 24; randomised patients", which does not present the number of adjusted NMAs that were conducted. Changing the reference to the proposed amendment would	ERG agree and will change reference to: (CS; Table 12-13, Document B Appendix D)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		accurately reference the number of adjusted NMAs that were conducted.	
5. On page 12 of the ERG report, two figures are missing from the references when describing "The results (CS; Table 14 Document B & CS Clarification Document Figure 25) – indicate there were no statistically significant differences between guselkumab and other subcutaneous biological treatments across any of the safety measures (AE, SAE WDAE)…"	We kindly request that the referenced table: (CS; Table 14 Document B & CS Clarification Document Figure 25) be changed to (CS; Table 14 Document B & CS Clarification Document Figure 25, 27, and 29).	The figure currently being referenced from the company's clarification document is the results for AEs. Since the other safety measures (SAE and WDAE) are being described, it would be beneficial to add figures 27 and 29 from the clarification documents to accurately reflect the results from all safety measures that were analysed.	ERG agree and will change reference to: (CS; Table 14 Document B & CS Clarification Document Figure 25, 27, and 29)
6. For Errata 5 stated in Appendix 1 on page 30 of the ERG report, we thank you for addressing this Errata, and we accept the change in title to "League table summary of relative risks for the PASI 75 response at the end of induction analyses; unadjusted; restricted evidence network." However, the figure being referenced is incorrect (CS; Table 15 of the clarification response).	We kindly request that the referenced table: CS; Tables 15 of the clarification Response be changed to CS; Figure 15 of the clarification table.	The table currently being referenced is the "Summary of pairwise comparisons with guselkumab from unadjusted relative effects analyses", which does represent the full results for the PASI 75 league table. Changing the reference to the proposed amendment would be an accurate reference to League table summary of relative risks for the PASI 75 response at the end of induction analyses; unadjusted; restricted evidence network.	ERG agree and will change reference to: (CS; Figure 15 of the clarification table).

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
7. For Errata 2 of Appendix 1, the ERG state "CS; Figure 25 of clarification document response should be identical to Figure 16 Doc B, but the treatments appear in a different order with some confidence interval estimates changing slightly. All differences are minor and do not change any key outcomes."	This is incorrect, these should not be identical because the results presented in Document B, Figure 16 are based on the full evidence network analysis (where all treatments, licensed and non-licensed were included in the full network NMAs, but treatments that were not of interest were omitted from the presentation of results) and the results presented in Figure 25 of the clarification document are based on the restricted network NMA (where NMA was run on treatments licensed in the UK).	The ERG is misinterpreting the results from Document B and the clarification document. However, the differences are minor and do not change the key outcomes	ERG would kindly request all diagrams are accurately described and labelled to avoid potential misinterpretation. With this additional information, ERG agrees to remove Errata 2 of Appendix 1.
8. For Errata 3 of Appendix 1, the ERG state "Pairwise comparisons of safety data in CS; Table 14 Doc B do not match adjusted safety NMA output in the clarification responses (CS; Figures 25, 27 & 29 clarification document). The difference in WDAE between guselkumab and infliximab is no longer significant. Whilst most changes are small, the ERG is unsure why any values have changed."	These results should not exactly match since the results presented in Document B Table 14 are based on the full evidence adjusted NMAs (where all treatments, licensed and non-licensed were included in the full network NMAs, but treatments that were not of interest were omitted from the presentation of results).	The ERG is misinterpreting the results from Document B and the clarification document. However, the differences are minor and do not change the key outcomes	ERG would kindly request all tables are accurately described and labelled to avoid potential misinterpretation. With this additional information, ERG agrees to remove Errata 3 of Appendix 1.
9. For Errata 4 of Appendix 1, the ERG state "Erelzi (etanercept biosimilar) appears in CS; Figure 28 and 29 of clarification document response (WDAE NMA) but it should not be	As stated in the clarification document, Erelzi was considered in the restricted network set of treatments for the restricted NMAs (CS; Table 9, Clarification Document) and had available data for PASI 75, IGA/PGA 0/1, and WDAE (CS; Table 8, Document B Appendix D),	The ERG is misinterpreting the results from Document B and the clarification document. However, the differences are minor and do not change the key outcomes	Due to the inconsistency of the inclusion of Erelzi in the analyses, the ERG assumed it should not appear in any analyses. ERG will update Errata 4 to: Erelzi was

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
included here. Erelzi also features in CS; Figure 9 of company's clarification document response."	therefore it was included in these NMA analyses. Erelzi was mistakenly not included in Table 14, Figures 14-15 of document B when reporting results from the full network which omitted treatments that were not of interest (which may have caused this Errata to be stated).		mistakenly not included in Table 14, Figures 14-15 of document B when reporting results from the full network which omitted treatments that were not of interest.
10. For Errata 6, additional errors identified in Tables	It should be noted that these were transcription errors in the Company submission documents. The correct values, as reported in the 'Correction' column in the table for Errata 6 was used in the NMAs.	The figures included in the correction column accurately capture the values.	The ERG is thankful for the confirmation that all values were input into the NMA correctly. Not a factual inaccuracy by the ERG, no change made.

Issue 5 Clinical effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 7 the ERG report states: *Post-randomisation PASI 90 response rates obtained after two visits were also higher for guselkumab (54.1%) compared to the ustekinumab (23.3%) in the NAVIGATE trial (CS; Table 13, Document B)."*	Suggest changing the phrasing to: *Post-randomisation PASI 90 response rates obtained on **more than** two visits were also higher for guselkumab (54.1%) compared to the ustekinumab (23.3%) in the NAVIGATE trial (CS; Table 13, Document B)."*	This current statement suggests that it took two visits for patients to achieve a PASI 90 response and more patients in the guselkumab group achieved this; whereas the endpoint is referring to the total number of visits that patients achieved PASI 90 response.	The ERG accepts the suggested phrasing of the sentence.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 8 the ERG report states: *"The ERG encountered a lack of clarity in the reporting of PASI 90 at trial visits in the NAVIGATE trial within the CS (Table 13, Document B) and considers that the PASI 90 response rate at 28 weeks reported in the published (NAVIGATE) article to be a more appropriate study endpoint."*	Suggest changing the phrasing to: *"The ERG has concerns over the relevance of reporting PASI 90 at trial visits in the NAVIGATE trial within the CS (Table 13, Document B) and considers that the PASI 90 response rate at 28 weeks may have been a more appropriate study endpoint."*	The current statement suggests the presentation of data from NAVIGATE lacks clarity which is not the case. Table 13, Document B provides the predefined primary and major secondary endpoint data for the NAVIGATE trial. The PASI 90 response rate at 28 weeks is not reported in the published (NAVIGATE) article.	The ERG accepts the suggested phrasing of the sentence. However the ERG kindly points out that the PASI 90 response at 28 weeks is in fact reported in Table 2 of the paper *Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase III NAVIGATE trial.*
On page 11 the ERG report states: *"The design of NAVIGATE made a direct comparison between ustekinumab and guselkumab difficult, with the company submission only presenting data for weeks 16-40 of the trial meaning patients were on guselkumab for longer than the license would recommend. The ERG requested detailed information on AEs from NAVIGATE for weeks 16-32 as a clarification, however the company provided the*	Suggest changing the phrasing to: *"The design of NAVIGATE made a direct safety comparison between ustekinumab and guselkumab over weeks 16-40 and weeks 16-60 of the trial, a period over which patients received two induction and two (weeks 16-40) or three (weeks 16-60) maintenance doses of guselkumab. The ERG requested detailed information on AEs from NAVIGATE for weeks 16-32 as a clarification, however the company provided the information for the period of 16-40 weeks in their response."*	The dosing adopted in the NAVIGATE trial was aligned with guselkumab license terms: The recommended dose of guselkumab is 100mg by SC injection at Weeks 0 and 4, followed by a maintenance dose every 8 weeks. 1 It should also be clear that this paragraph is referring to safety data as primary and major secondary endpoints were based on data from Week 28 to Week 40.	The dosage under consideration for this

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
information for the period of 16-40 weeks in their response."			guselkumab appraisal is as follows (CS; Table 2 Doc B: Wk 0 – Induction Dose Wk 4 – Induction Dose Wk 12 – Maintenance Dose Wk 16 – Assessment of Efficacy. Stop treatment if no response. Wk 20 – Maintenance Dose The ERG was seeking safety data from NAVIGATE to compare to the VOYAGE trials, which reported safety data at 16 weeks, The ERG was keen to maximise the relevant safety information when assessing the safety of guselkumab, a drug not previously routinely available. However the safety data presented by the company meant it included a longer follow-up period and that subjects could have had an additional dose of guselkumab, hence it was not directly comparable. The ERG accepts the proposed textual change.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG has misinterpreted the study design of NAVIGATE trail and made inaccurate conclusions about safety profile of guselkumab. Page 11: *"Whilst these events are mostly minor in severity, there is a consistent pattern suggesting a slightly inferior safety profile for guselkumab compared to ustekinumab."*	We kindly request that this statement is removed.	As explained in the company submission, NAVIGATE is not a head to head trial against ustekinumab. NAVIGATE studied the efficacy of guselkumab in patients that have not responded to ustekinumab (primary non-responders), therefore it is not appropriate to draw conclusion on the safety differences based on NAVIGATE study. The results from the safety NMAs (presented in Table 14 of CS, Figure 25, 27 and 29 of the Company Clarification Question reply) do not show statistically significant differences between the safety profile of guselkumab and ustekinumab.	Whilst the ERG is aware that NAVIGATE is not designed as a head-to-head trial, however subjects were randomised and ERG feels some comparison can be made. ERG has rephrased as follows: Page 11: *"Whilst these events are mostly minor in severity, there is a consistent pattern suggesting a slightly inferior safety profile for guselkumab compared to ustekinumab in patients previously treated with ustekinumab."*

Issue 6 Comments to the revised company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Cost comparison differentiating clinical similarity Page 2:. "*In effect it is assumed that after 2nd line the costs incurred will be similar between sequences."*	Remove the analysis from ERG supplementary report.	The ERG sequencing analysis incorrectly assumes that there are no further costs after a patient discontinues 2nd line treatment. This is clinically implausible and methodologically incorrect (Please refer to Issue 2: Methodological limitations of the cost comparison). If we run a sensitivity analysis with the least costly biologic therapy in third line, which is etanercept biosimilar (£8,528[redacted].	Not a factual inaccuracy by the ERG, no change made.
ERG has failed to acknowledge that it has previously used infliximab as a third line biologic in treatment sequence to inform the NICE decision problem relating	Please acknowledge that infliximab has been used previously as a third line biologic in treatment sequence to inform the NICE decision in TA 442 (Ixekizumab).	The same ERG has previously presented treatment sequence with infliximab in third line position after 2 lines of biologic therapy (please refer to NICE TA 442, Ixekizumab). Although infliximab is generally used in very severe patients. It is clinically plausible that patients who have failed two biologics are likely to be very severe patients.	Not a factual inaccuracy by the ERG, no change made.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
to TA 442 (Ixekizumab). Page 2: "*Guselkumab is being assessed for use among the moderate to severe. NICE has only approved infliximab for the very severe.* *The ERG is sceptical of the assumption that the 3rd line treatment will be infliximab."*			
ERG has failed to consider the sensitivity analysis presented by the company to address differences	Please remove this statement or include results of the sensitivity analysis.	In its revised company submission, Janssen presented a sensitivity analysis (Table 3, scenario 5 of the revised company submission) that explored the impact of change in cost of infliximab on the overall cost of treatment sequence.	As noted in the ERG commentary the ERG has not parsed the 2nd company model but disagrees with the apparent

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
between induction and maintenance cost of infliximab. Page 4: "*The revised company model also appears to apply the higher 1st year induction costs of infliximab to all years. This further biases results in favour of guselkumab."*			model structure and assumptions around the 3rd line treatment. There is a scenario analysis listed as described by the company but given the main ERG concerns about the apparent model structure the ERG has not taken this further. The lack of documentation of the 2nd model hampers any summary or critique of the company base case and scenario analyses. Not a factual inaccuracy by the ERG, no change made.

Guselkumab for treating moderate to severe plaque psoriasis [ID1075]

List of errata pages

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

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

[redacted]

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

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

The similarity of the patient distribution across PASI health states for guselkumab and ixekizumab at central NMA estimates means that similar proportions of patients would receive ongoing maintenance therapy and that any QALY estimates would be reasonably

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

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

The ERG did not have the opportunity to reproduce the NMA presented by the company and could only validate through a review of the presented input, output and WinBUGS code. The ERG verified the baseline and outcome data extracted from each trial in the NMA, as reported in CS; Document B Appendices Tables 7 and 8, respectively. Overall, the level of accuracy was high with most discrepancies expected to have minimal impact on the NMA. A

few larger inconsistences in the extracted data were found (see safety evidence below), however the ERG cannot tell if these errors are confined to the tables, or if they were carried

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

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

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

3.3 ERG's critique of safety evidence submitted

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

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

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

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

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

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

4.1 Company cost comparison

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

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

The company states that 5 years is sufficient to capture the majority of the costs of guselkumab, with around 30% of patients remaining on treatment at the end of the 5 years.

Appendix 1: Errata in company submission

The ERG have identified the following errors within the CS.

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

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

~~2.~~

~~3.~~

4. Erelzi (etanercept biosimilar) was mistakenly not included in Table 14, Figures 14-15 of document B when reporting results from the full network which omitted treatments that were not of interest.

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

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

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

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

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

3.2 ERG's critique of clinical effectiveness evidence submitted

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

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

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

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

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

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

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

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

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