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Committee presentation

Guselkumab for treating moderate to severe plaque psoriasis

1st Appraisal Committee meeting - FTA

Committee B

Chair: Sanjeev Patel

NICE technical team: Orsolya Balogh, Ian Watson

ERG: Warwick Evidence

1 February 2018

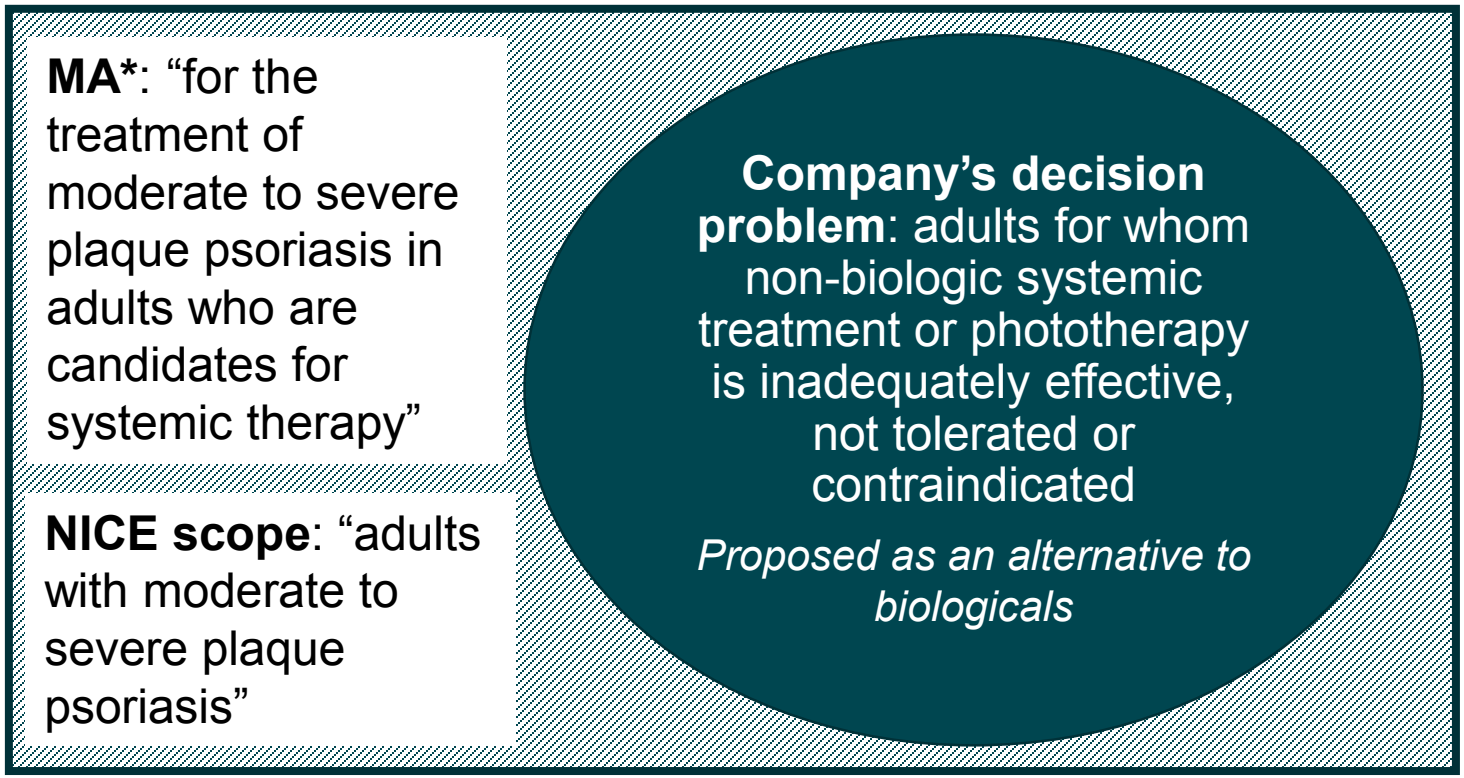
Key issues

- ***This topic is proposed as an FTA using cost comparison method***
  - 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 comparison of annual costs
  - 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 scope and MA - reflects likely position in clinical practice



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

***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, in 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

- Company presented *clinical comparison* vs all biologicals; and *cost comparison* vs adalimumab and ustekinumab

*PASI ≥10, DLQI ≥10

Market share – subcutaneous biologicals 2014–2017

- Adalimumab has a falling market share
- Ustekinumab has a reasonably constant market share over the period
- Secukinumab has a strongly growing market share

Comparators: NICE technology appraisals

Guidance	TA103: etanercept TA134: infliximab	TA146: adalimumab TA180: ustekinumab	TA350: secukinumab TA442: ixekizumab
Clinical effectiveness	• Key outcomes: PASI response rates (PASI75[§]), DLQI • TA442: PASI75 rates for comparators were 41–82%[+] • Ixekizumab was more effective than adalimumab and ustekinumab; 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
	• Consideration given to sequences of biologicals – sequencing analyses were uncertain, 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 – adults with psoriasis

- VOYAGE-1
- VOYAGE-2

placebo and active controlled (adalimumab) trials + open-label extension

- NAVIGATE

trial of switching to guselkumab vs ustekinumab after inadequate response to ustekinumab

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

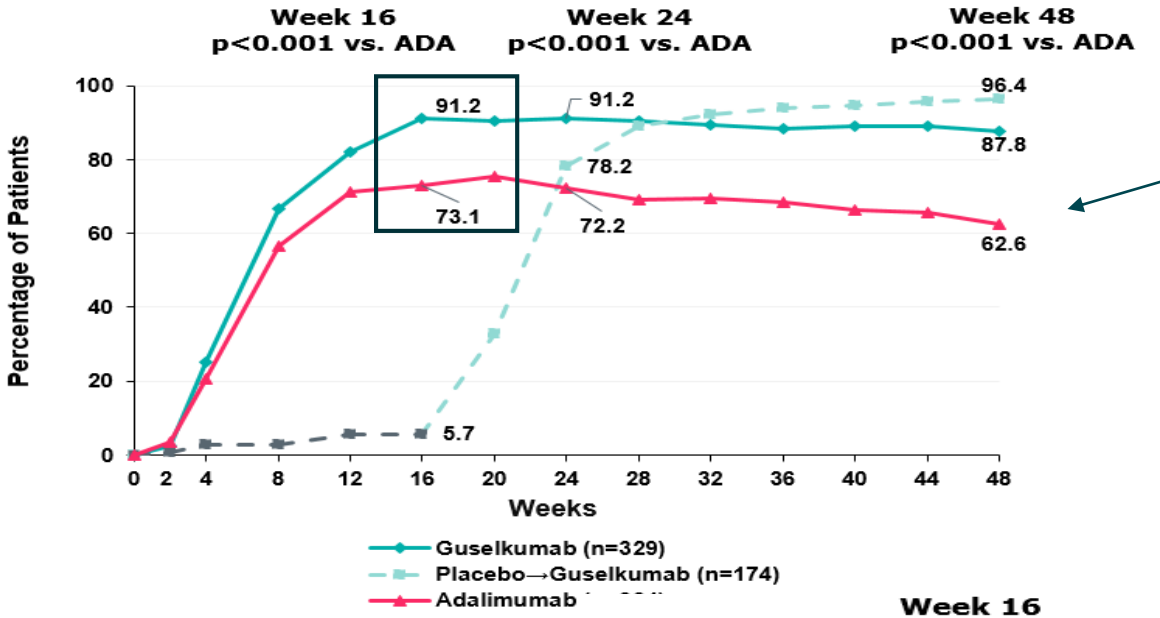
Network meta-analysis (NMA) – 45 randomised controlled trials

- Random effect model, adjusted for placebo response rate

- 2 sets of analyses: Full (all possible biologicals, including unlicensed) and restricted (only comparators in the decision problem)
  - Presented efficacy and safety outcomes
  - **ERG** considered the 'restricted NMA' to be more appropriate than the 'full NMA' and consistent with the final scope

PASI75 results of VOYAGE 1, VOYAGE 2

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

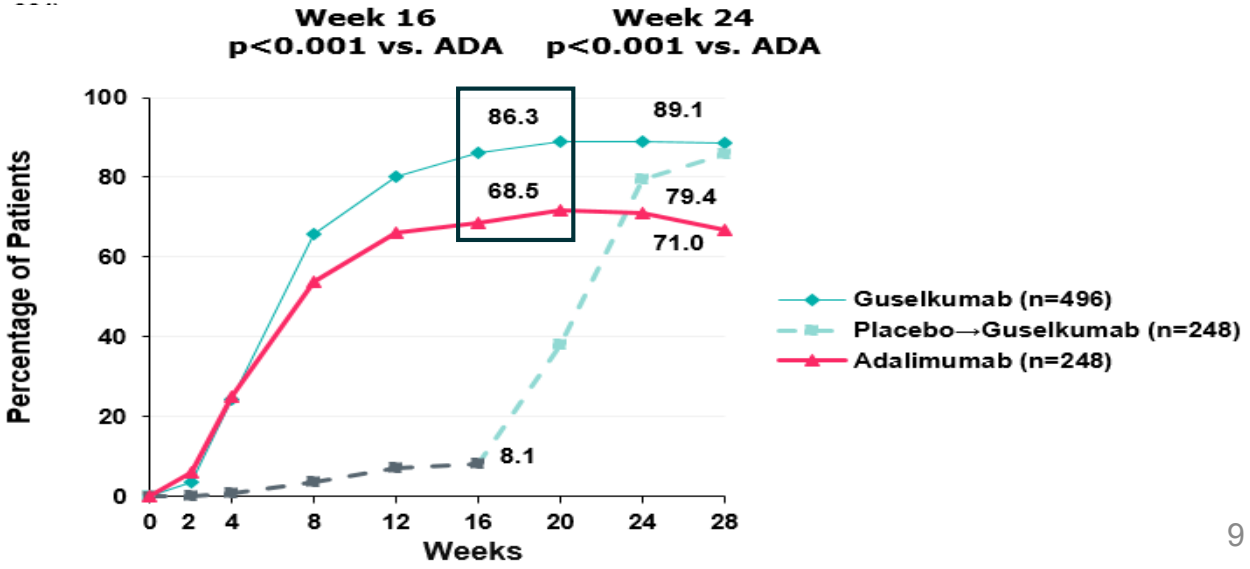


Voyage 1

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

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

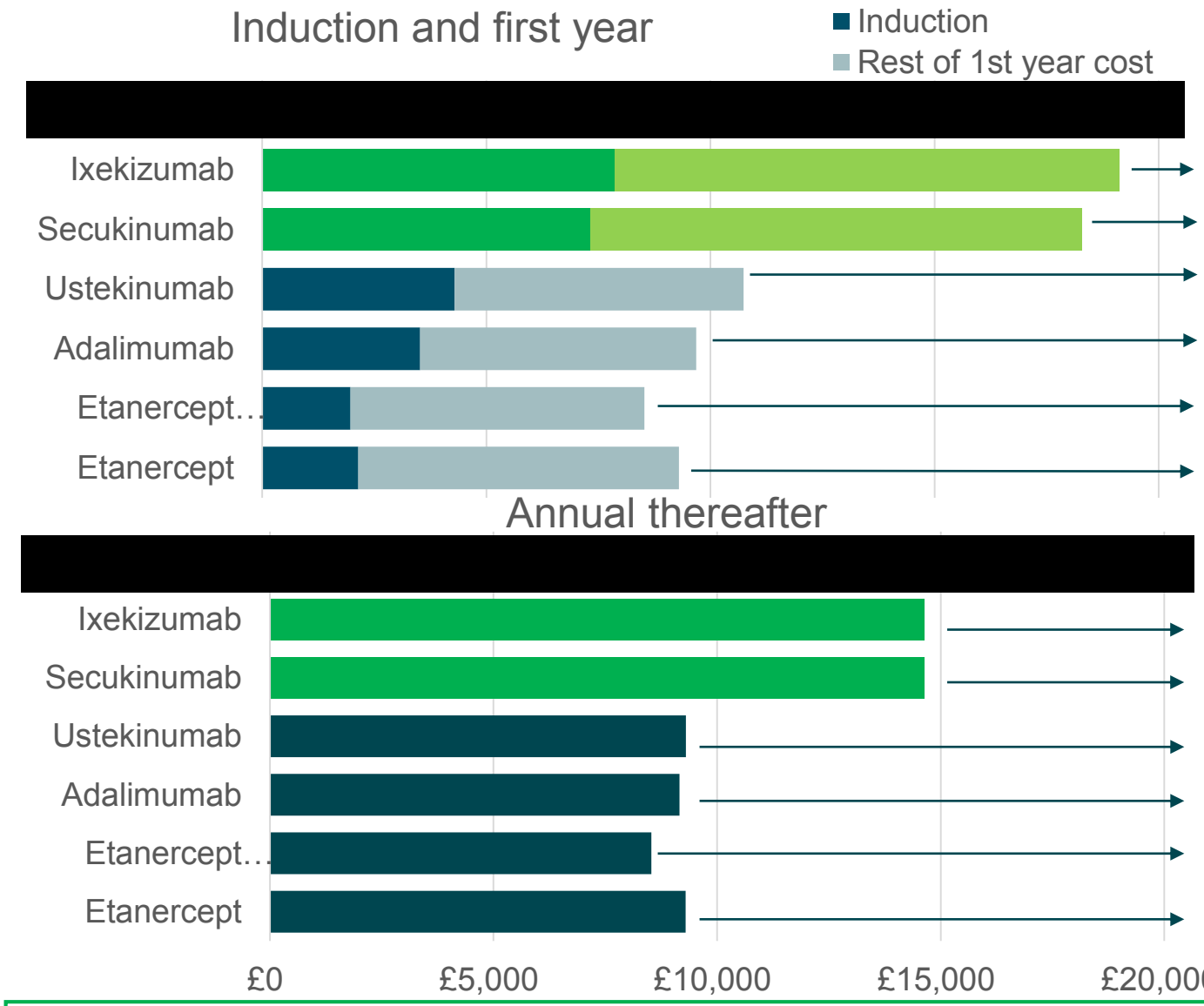
ERG review
Clinical effectiveness evidence

- Trials included a proportion of people (21%) who had previously received biological treatment
  - Adequately reflect the NHS population and the expected use of guselkumab
  - Comparator (adalimumab) appears to be less effective than anti-IL drugs
    - head-to-head comparisons of guselkumab with more effective biologicals not yet available
- 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

- ‘Antagonism of the IL23 pathway represents a step-change in the management of…moderate-to-severe psoriasis’
- ‘Newer biological agents have been welcomed, and provide people with more convenient therapy’
  - Highlighted that people who have lack of efficacy, drug resistance or failures have a particular need for new treatments
- ‘Hoped that [guselkumab] would provide improved clearance... Patients want to see clearance of all signs and symptoms of 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’
- ‘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



Induction	First year
£7,880	£19,130
£7,310	£18,280
£4,290	£10,740
£3,520	£9,680
£1,970	£8,530
£2,150	£9,300

Annual thereafter
£14,630
£14,630
£9,300
£9,160
£8,530
£9,300

Figures are rounded

Ixekizumab and secukinumab have confidential PASs - see part 2

Cost comparison analysis

- Company presented a cost comparison analysis comparing guselkumab with adalimumab and ustekinumab
  - Adalimumab and ustekinumab are the most widely prescribed 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 costs of treatment
  - Over 5 years
  - Taking into account discontinuation after induction treatment failure (assuming similar effectiveness) and long-term discontinuation

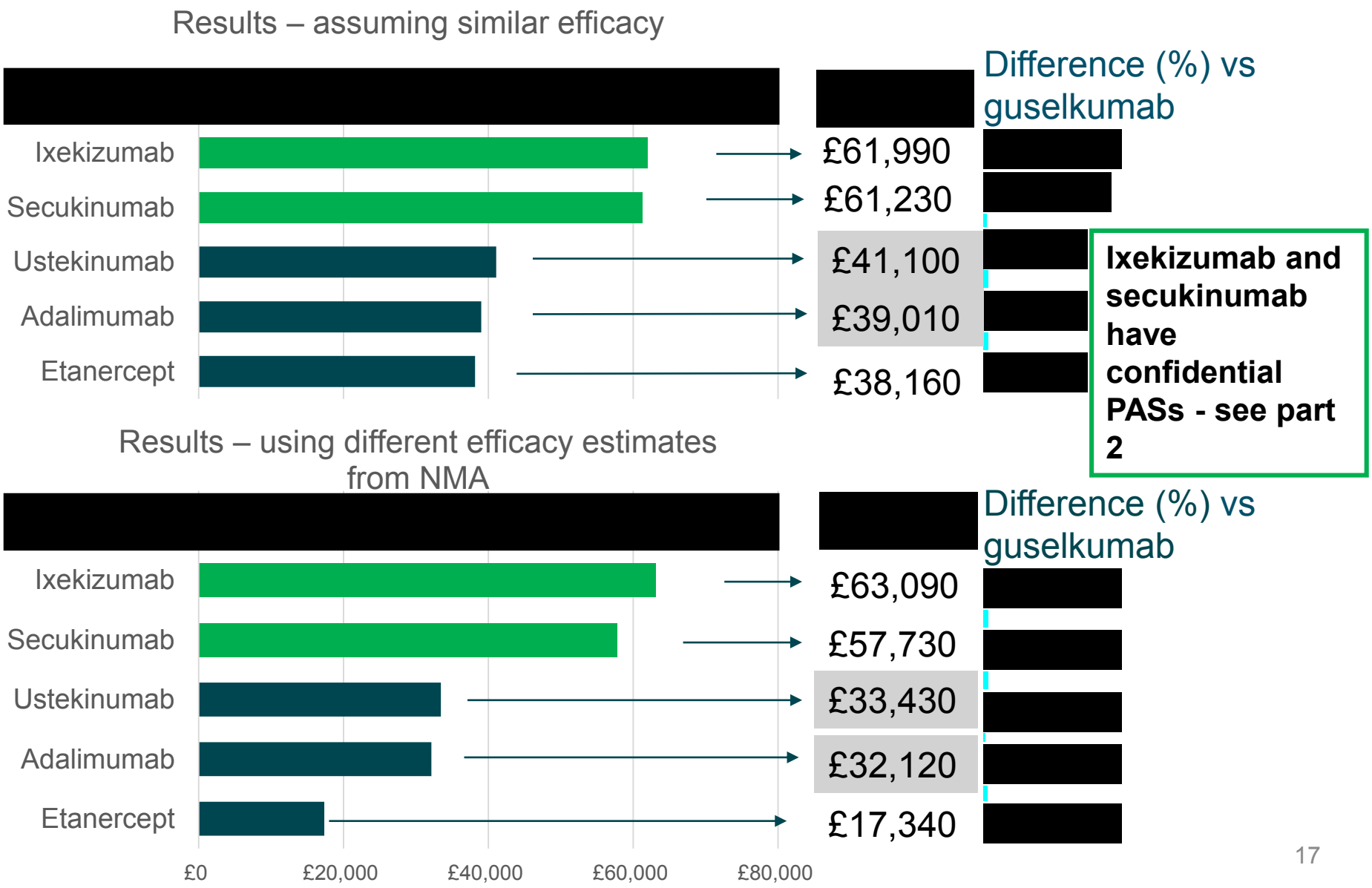
	Total cost	Difference vs guselkumab
Guselkumab		
Adalimumab	£25,790	
Ustekinumab	£27,930	

Figures are rounded

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
  - *ERG also presented scenario analyses (time horizon, long-term discontinuation); see ERG report section 4*

ERG exploratory analysis, 10 year costs



ERG review: additional comments

- Company analysis focuses on adalimumab and ustekinumab – although most commonly prescribed, adalimumab market share is declining 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 reasonable and growing market share – may be displaced by guselkumab
  - Ixekizumab appears to be the most effective biological, and guselkumab is similarly effective
    - Although market share is currently low, 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

Overview of technical team assessment

Decision problem: Adequate, potentially suitable for cost comparison FTA

- 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 and NMA: greater effectiveness than most biologicals, 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): guselkumab is [redacted] than ADAL, [redacted] than USTE
- ERG highlights that greater effectiveness would influence cost
  - Guselkumab appears more effective and [redacted] than ADAL and USTE *([redacted])*
  - 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 comparison of annual costs
  - Company analysis (assuming similar effectiveness) vs ADAL and USTE - guselkumab is [redacted] than ADAL and [redacted] than USTE
  - ERG exploratory analysis (using NMA effectiveness estimates)
    - vs ADAL/USTE - guselkumab is [redacted] and more effective
    - vs other comparators (including IXEK) - similarly effective, costs based on comparator PASs - *costs including all PASs to be shown in Part 2*

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*"