NICE National Institute for Health and Care Excellence

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Secukinumab for treating non-radiographic axial spondyloarthritis

Lead team presentation

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Company: Novartis

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Key issues (clinical effectiveness)

Issue 1: position of secukinumab in the treatment pathway

- How would secukinumab be used in clinical practice? Would it be used 1st and 2nd line?
- What are the comparators at these positions? **Key decision**
  - Are there any people who could have secukinumab but not a TNF-α inhibitor. What treatments would these people currently have?

Issue 2: network meta-analysis results

- Is secukinumab less clinically effective than the TNF-α inhibitors? **Key decision**
  - Are the sources of heterogeneity across studies included in the NMA identified by the company likely to bias the results against secukinumab? Is there any evidence of bias?

Issue 3: clinical effectiveness of secukinumab used as a 2nd line treatment after TNF-α inhibitors

- There are limited data for the clinical effectiveness of secukinumab used second line after a TNF-α inhibitor. Would it be expected to be similarly effective when used second line as first line?
- If a person had a TNF-α inhibitor as their first treatment would clinicians chose another TNF-α inhibitor or secukiniumab as the next treatment?

Uncertainties/ minor issues identified in the technical report: people in PREVENT had more severe disease (higher BASFI) than UK clinical practice

Secukinumab (Cosentyx, Novartis)

Marketing authorisation	Treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs)
Dosage and administration	Subcutaneous injection with a pen or pre-filled syringe. The recommended dose is 150 mg administered subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing.
Mechanism of action	Monoclonal antibody that binds to and neutralises the activity of the proinflammatory cytokine IL-17A
Average list price per course of treatment	£1,218.78 for 2 x 150 mg x1 and 300mg 2ml x 1 <u>Annual cost of treatment</u> First year: £9,750.24 Subsequent years: £7,312.68 A confidential discount on the price has been agreed.

Non-radiographic axial spondyloarthritis

- Axial spondyloarthritis (axSpA) is a chronic rheumatic condition, characterised by inflammation at the sacroiliac joint and spine. AxSpA is an umbrella term, encompassing:
  - Radiographic (**rad-axSpA**) (also known as ankylosing spondylitis (AS)) where inflammatory changes in the sacroiliac joints or spine can be determined on X-ray
  - Non-radiographic (**nr-axSpA**) with absence of visible structural damage on X-ray, although inflammation may be observed on MRI
- AxSpA affects ~ 0.1-0.4% of the general population. It is estimated around 62,650 people live with nr-axSpA and 100,815 with rad-axSpA in England
- Inflammation at axial joints can lead to dysregulation of bone maintenance which may result in changes to structure and function
- The tumor necrosis factor (TNF)-alpha and interleukin (IL)-17 cytokine families play a key role in symptom production and are important therapeutic targets
- Risk increases significantly in people with the human leukocyte antigen-B27 (HLA-B27) gene. Children are twice as likely to develop condition if they have inherited the gene
- Common symptoms include chronic back pain, stiffness, fatigue, poor sleep quality and night-time waking. Joint and tendon pain, stiffness, fatigue, arthritis and swelling of the fingers are also common, resulting in significantly reduced physical function
- No cure, treatment aims to relieve pain and stiffness, prevent joint and organ damage and preserve joint function and mobility

Patient and carer perspectives

- AxSpA is a painful and debilitating condition characterised by periods of fluctuating intensity, leading to slowly increasing spinal and peripheral joint damage
- Up to 25% of people with axSpA eventually develop complete fusion of the spine which leads to substantial disability and restriction
- The disease burden of AxSpA is variable, many people live active and rewarding lives, others experience progressive spinal pain, immobility and functional impairment
- Most people with axSpA live a normal lifespan but there is an increased risk of premature death from cardiovascular disease.
- More than 50% of people who are affected have work instability. The average age of diagnosis is 24, a prime time for establishing a career.
- Many experience depression, fatigue and poor sleep during their lives, all of which exert a profound influence on quality of life

Perspectives on secukinumab

- Reduces pain, fatigue and disability. Improves mobility, and quality of life and productivity
- Secukinumab may improve quality of life, especially if it can be used at an early stage. There is also an opportunity to slow down disease progression if treatment starts at an earlier stage, before a person has progressed to radiographic changes which are irreversible.
- Secukinumab provides an alternative treatment for patients whose treatment has failed with anti-TNF inhibitors in nr-axSpA and has a new mode of action for treatment of disease.

Treatment pathway

NICE guideline 65 spondylarthritis in over 16s: diagnosis and management

Non–radiographic **axSpA**

Offer physical therapy

↓

Non steroidal anti-inflammatory drugs (NSAIDS)

↓

TNF-α inhibitors
adalimumab* TA 383 (2016)
certolizumab pegol TA383
etanercept* TA383
golimumab TA497 (2018)
Stopping rule at 12 weeks
Secukinumab?

↓

Repeat with another TNF-α inhibitor (if disease has not responded, stops responding or if first TNF-α inhibitor not tolerated (TA383))
Secukinumab?

Radiographic **axSpA**

Non-pharmacological interventions (exercise and physiotherapy)

↓

Inadequate response or intolerance to NSAIDs

↓

TNF-α inhibitors
adalimumab* TA383
certolizumab pegol TA383
etanercept* TA383
golimumab TA383
Infliximab (if treatment is started with least expensive infliximab product) TA383
Secukinumab TA407 (2016)

↓ Inadequate response or intolerance

Repeat with another TNF-α inhibitor (if disease has not responded, stops responding or if first TNF-α inhibitor not tolerated (TA383)
Secukinumab TA407

* Since guidance, biosimilar products are available

Company comments on place of secukinumab in the treatment pathway

Company:

- Marketing authorisation does not limit use of secukinumab to a particular line of treatment. Secukinumab should be a 1st or 2nd line option.
- Some people contraindicated to TNF-α inhibitors, such as people with MS and risk/history of TB infection.
- More than 45% of patients with nr-axSpA treated currently with TNF-α inhibitors are not responding to treatment.
- UK clinical expert advice suggests switching to a biologic with a new mechanism of action following primary failure may be more effective than switching within class.

ERG:

- Unlikely that secukinumab would be the 1st-line biologic for most people; likely to be used 2nd-line (in patients who did not respond at all to their first TNF-α inhibitor) or as a last-line biologic (in patients who had some response to TNF-α inhibitors).
- Population in PREVENT (regulatory trial of secukinumab for nr-axSpA) may not reflect population for whom it will be used in clinical practice.

Decision problem

	NICE scope	Company submission	Rationale for difference
Population	People with nr-axSpA with objective signs of inflammation, whose disease has responded inadequately to, or who are intolerant to, NSAIDs	As per scope	N/A
Comparators	• Adalimumab • Certolizumab pegol • Etanercept • Golimumab • Established clinical management without biological treatments	As per scope (secukinumab compared with individual TNFα inhibitors and TNF-α inhibitors as a drug class)	N/A
Outcomes	• Disease activity • Functional capacity • Disease progression • Pain • Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • Symptoms of extra-articular manifestations Adverse effects of treatment • Health-related quality of life	As per scope, except for peripheral arthritis, dactylitis, and symptoms of extra-articular manifestations.	The outcomes not included were not measured outcomes in the PREVENT trial

Definition: disease activity/function measures

ASAS: Assessment of SpondyloArthritis International Society
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
BASFI: Bath Ankylosing Spondylitis Functional Index
BASMI: Bath Ankylosing Spondylitis Metrology Index

ASAS	BASDAI	BASFI	BASMI
• Patient assessment of disease activity/back pain VAS • Function using 10 BASFI questions • Inflammation using 2 BASDAI questions • Spinal mobility (BASMI lateral spinal flexion assessment) • C reactive protein	6 questions (0–10 scale on a VAS) pertaining to the 5 major symptoms of AS: • fatigue, spinal pain • joint pain /swelling • areas of localised tenderness • morning stiffness duration • morning stiffness severity	10 questions (0–10 scale on a VAS) • 8 questions consider activities related to functional anatomy • 2 questions assess the patients' ability to cope with everyday life	• Number of measurements to define clinically significant changes in spinal movement

Definition: response measures

ASAS 40 (primary outcome in PREVENT trial)	BASDAI 50 (response measure in the economic modelling)	BASDAI 50 + spinal pain VAS (stopping criteria for TNF-α inhibitors & secukinumab in NICE guidance)
Improvement of ≥40% and ≥2 units in ≥ 3 of the 4 main domains of ASAS and no worsening in the remaining domains	Improvement of ≥ 50% in the BASDAI compared with baseline	BASDAI 50 or reduction in BASDAI by ≥ 2 units and reduction in the spinal pain VAS by ≥2 cm

Primary clinical evidence: PREVENT

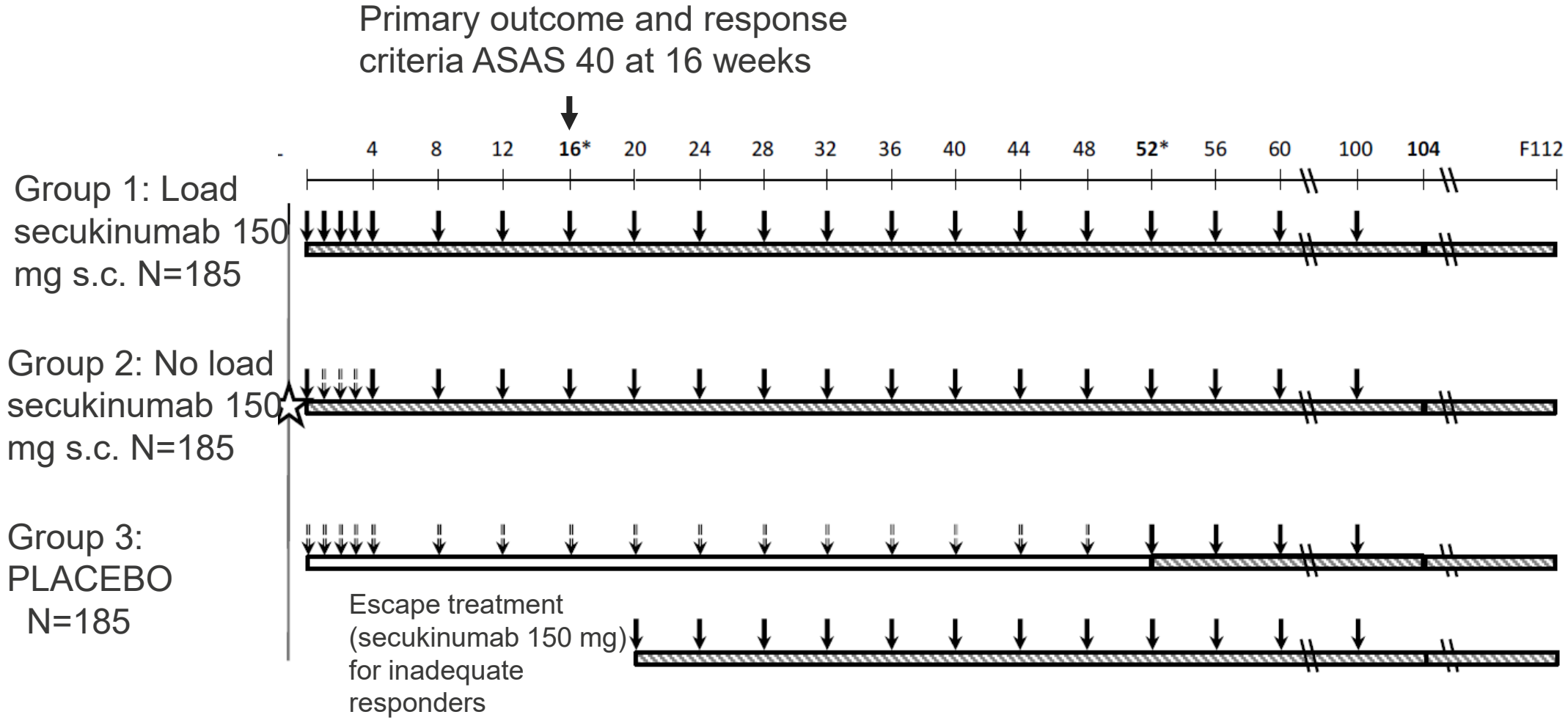
Design	Phase III, double-blind, randomised, multicentre
Location	International: 140 sites in 24 countries; 9 sites in UK (**n=24**)
Population	Adults fulfilling the ASAS classification criteria for axSpA plus an abnormal CRP and/or MRI, with no radiographic evidence of changes in the sacroiliac joints that would meet the modified New York criteria for rad-axSpA (**n=555**) **~90% of trial population were TNF-α inhibitor naïve** **~10% had exposure to 1 previous TNF-α inhibitor**
Intervention	Secukinumab (with load dose) (**n=185**) Secukinumab (without load dose) (**n=184**) (secukinumab MA includes loading dose)
Comparator	Placebo (**n=186**)
Outcomes	**Primary outcome:** • Proportion of **TNF-α inhibitor naïve** patients achieving an ASAS40 response (disease activity) at Week 16 **Secondary outcomes:** • Disease activity • Functional capacity • Adverse effects of treatment • Health related quality of life (including EQ-5D)

PREVENT eligibility criteria

- Diagnosis according to Assessment of SpondyloArthritis International Society(ASAS) AsSpA criteria
  - Inflammatory back pain≥ 6 months
  - Onset before 45 years of age
  - Imaging/inflammation markers
    - Sacroiliitis on MRI with ≥1 SpA feature OR HLA-B27 positive with ≥2 SpA features
    - Objective signs of inflammation at screening, evident by either MRI with sacroiliac joint inflammation and/or hsCRP >ULN
  - Disease activity/pain
    - Active axSpA as assessed by BASDAI ≥ 4 cm (0–10 cm) at baseline
    - Spinal pain as measured by BASDAI question #2 ≥4 cm (0–10 cm) at baseline
    - Total back pain as measured by VAS ≥40 mm (0–100 mm) at baseline
- People who have been on a TNFα inhibitor (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for ≥3 months prior to randomisation or have been intolerant to at least one administration of an anti-TNFα agent (~10% in trial had previous treatment)

PREVENT trial design

Followed people for up to 52 weeks. Responders at 16 weeks continued treatment
Marketing authorisation: discontinuation should be considered if no response at 16 weeks
NB only extrapolated 16 week data from no load group was used in economic model



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PREVENT statistical analysis plans

2 plans

  - EMA (**secukinumab with load dose**) regulatory submission. Primary outcome measured at week 16
  - FDA (**secukinumab without load dose**) regulatory submission with primary outcome measured at week 52.

- Analysis set: FAS (analysable patients from the randomised set to whom study treatment had been assigned)
- Tested for superiority secukinumab 150mg load regimen vs. placebo regimen using non-responder imputation.
- Pre-planned subgroups (not statistically powered):
  - Objective signs of inflammation (CRP+ and MRI+; CRP+ and MRI–; CRP– and MRI+)
  - Previous biological treatment experience TNFα-naïve; TNF-IR (inadequate response)

PREVENT patient baseline characteristics

Trial stratified by CRP and MRI status, most people had not had a previous TNF-α inhibitor

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Placebo N=186	Total N=555
Demographics				
Age, years, mean ± SD	39.1 ± 11.45	39.8 ± 11.68	39.3 ± 11.47	39.4 [redacted]
Gender, female, n (%)	105 (56.8)	100 (54.3)	95 (51.1)	[redacted]
Disease indicators				
Sacroiliac joint inflammation on MRI by history or current, n (%)	132 (71.4)	134 (72.8)	139 (74.7)	[redacted]
CRP and MRI status, n (%)				
CRP+ and MRI+	[redacted]	[redacted]	[redacted]	166 (29.9)
CRP+ and MRI–	[redacted]	[redacted]	[redacted]	154 (27.7)
CRP– and MRI+	[redacted]	[redacted]	[redacted]	235 (42.3)
TNF-α inhibitors experienced, n (%)	21 (11.4)	18 (9.8)	15 (8.1)	54 (9.7)

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PREVENT: baseline disease activity + function

- Characteristics balanced across treatment arms
- ERG: baseline BASFI scores (around 6) are higher than European registry data and clinical trials of TNF-α inhibitors (~5.0 to 5.5).
- Company: High baseline BASFI may effect clinical effectiveness results for secukinumab because lower BASFI is considered a good predictor of response.

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Placebo N=186	Total N=555
BASFI				
Mean ± SD	6.244 ± 2.0392	5.922 ± 2.0345	5.893 ± 1.8998	[redacted]
BASDAI				
Mean ± SD	7.082 ± 1.3307	6.931 ± 1.4494	6.760 ± 1.2422	[redacted]
BASMI (linear)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]

PREVENT primary endpoint: ASAS40 response in TNF-α inhibitor naïve patients

- Using non-responder imputation at week 16; FAS, secukinumab increases the proportion of people having an ASAS40 response compared with placebo
- Secukinumab with loading dose (licensed treatment) and without loading dose similarly effective against placebo

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Secukinumab 150 mg Load (N=164)	68/164 (41.5)	vs placebo	1.72	[redacted]	0.0197
Secukinumab 150 mg No Load (N=166)	70/166 (42.2)	vs placebo	1.76	[redacted]	0.0146
Placebo (N=171)	50/171 (29.2)	N/A			

ERG analysis of main PREVENT outcomes in all patients

- The ERG summarised odds ratios or mean difference between secukinumab with load arm compared with placebo in all patients
- [redacted].

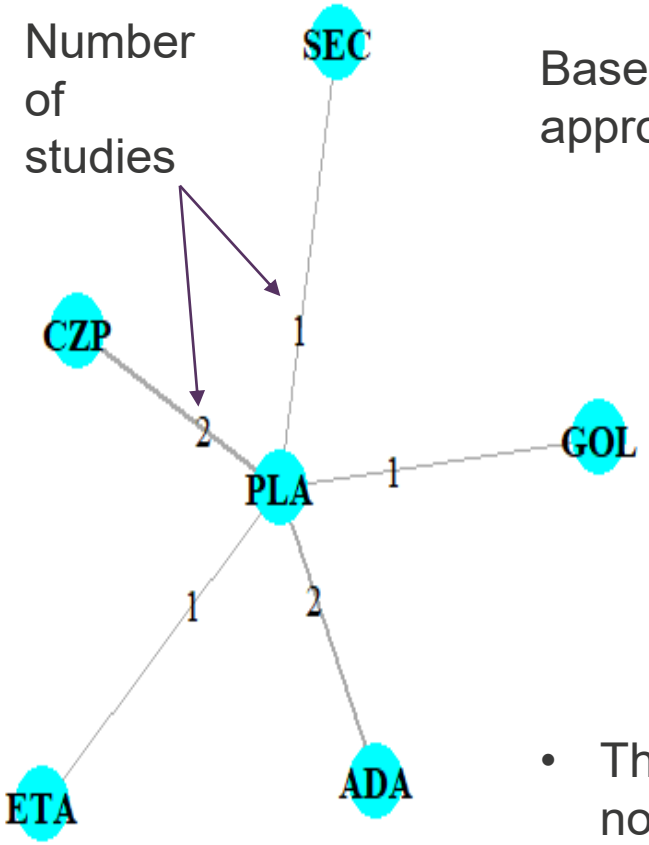
Outcome	Odds ratio (OR) or mean difference (MD)	95% Confidence interval
ASAS 40	OR 1.77	[redacted]
BASDAI 50	OR [redacted]	[redacted]
BASFI *	MD [redacted]	[redacted]
EQ-5D (change from baseline)	MD [redacted]	[redacted]

* A decrease in BASFI is a decrease in functional impairment

Source: table 3, ERG report page 28

Company network meta-analyses (NMA)

- No head-to-head trials of secukinumab vs. TNF-α inhibitors
- Company's NMA included 7 RCTs at 16 weeks and outcome data for (i) ASAS40, (ii) BASDAI50, (iii) BASDAI change from baseline (CFB), and (iv) BASFI CFB (these outcomes were included in the economic model). Numbers are number of studies.



Base-case NMA in the company model was based on the joint modelling approach used in TA383 and incorporated following aspects:

- A joint model takes in account relationships between outcomes when synthesising evidence. In this case by modelling changes in BASDAI and changes in BASFI as correlated, and by functionally relating BASDAI 50 to changes in BASDAI from baseline.
- Mean scores at baseline were estimated for placebo and for all treatments. ERG tested alternative BASDAI baseline scores
- Only fixed effects models were fitted, that is between-study heterogeneity was not considered
- Results estimated for secukinumab vs. individual TNF- α inhibitors and for secukinumab vs TNF- α inhibitors

- The ERG re-conducted the NMA by using data from the pooled load and no-load arms of secukinumab in PREVENT and included the results in its base-case analysis.

ADA=adalimumab, CZP= certolizumab pegol, ETA= etanercept, GOL=golimumab, PLA= placebo and SEC= secukinumab.

NMA results for secukinumab compared to other treatments

[redacted]

	Outcome	BASDAI50 Response
Comparator		Odds Ratio
Adalimumab	Mean	[redacted]
	95% CrI	[redacted]
Certolizumab pegol	Mean	[redacted]
	95% CrI	[redacted]
Etanercept	Mean	[redacted]
	95% CrI	[redacted]
Golimumab	Mean	[redacted]
	95% CrI	[redacted]
TNF-α Inhibitors (Class)	Mean	[redacted]
	95% CrI	[redacted]
Conventional Care	Mean	[redacted]
	95% CrI	[redacted]

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Source: Table 11, ERG report (page 50-51)

Uncertainties in the NMA

- Company identified the following uncertainties, which it said may affect results, but data limitations meant not possible to quantify the influence/impact of potential treatment-effect modifiers on results. Overall company did not expect clinical effectiveness to differ between secunkinumab and TNF-α inhibitors, used NMA results in model.
  - Placebo response rates varied across studies (attempts made to adjust for higher placebo response rates in PREVENT but inconclusive)
  - Differences in baseline characteristics
    - baseline BASFI
    - HLA-B27
    - CRP levels,
    - % who had previously received a TNF-alpha inhibitor,
    - % who were MRI-/CRP-
  - Some trials included people with rad-axSpA in the nr-axSpA arm
  - Studies used different missing value imputation methods
  - Evidence base was small without any head-to-head trial information
  - Trials had different methods to account for trial discontinuation
- **ERG**: should not presume heterogeneity explains [redacted] with secukinumab. Combining load/no-load dose arms from PREVENT unlikely to affect expected results, but it could reduce uncertainty around the treatment effect of secukinumab compared to TNF-α inhibitors.

Key issues (clinical effectiveness)

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Uncertainties/ minor issues identified in the technical report: people in PREVENT had more severe disease (higher BASFI) than UK clinical practice

Key issues (cost-effectiveness)

1 Costs assumed for TNF-α inhibitors : major impact on cost effectiveness

- As costs for TNF-α inhibitors are the key driver of cost effectiveness analyses, should the least expensive nationally available TNF-α inhibitor (adalimumab biosimilar) be used to represent the class at 1st line OR
- Should the company's approach of using market share of TNF-α inhibitors be used?

2 Conditional baselines: area of uncertainty

- Whether baseline BASDAI and BASFI response should be conditional on response is an area of uncertainty which significantly impacts cost-effectiveness estimates. Both company and ERG use conditional baselines but the committee for TA383 preferred the use of a common baselines. What is the committee's preference for this appraisal?

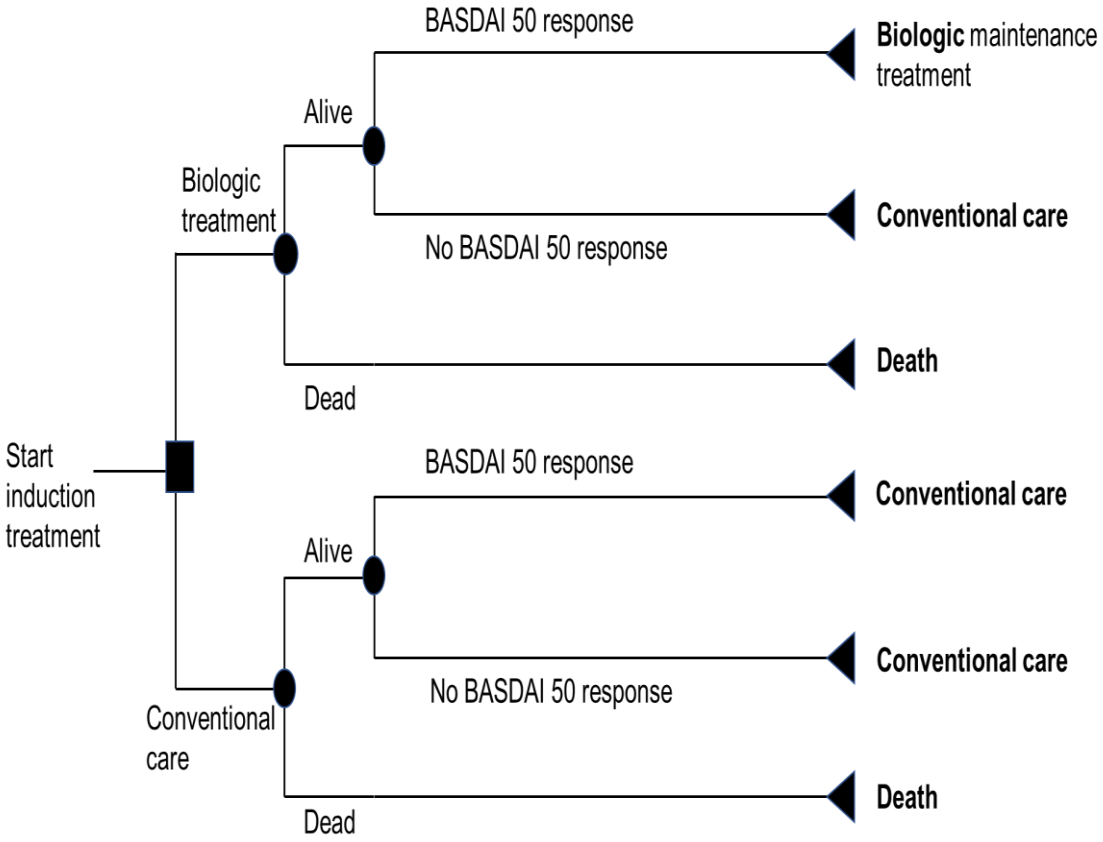
3 Subsequent treatments : area of uncertainty and relates to 2

- Company base case model does not consider subsequent treatment with biologics when considering 1st-line use of secukinumab. However, modelling of patients' BASFI and BASDAI scores is incorrect in sequence model and it can only be used if common baselines are considered. ERG base-case uses the non-sequence model with conditional baselines. Which approach is appropriate for decision-making?
- Additional uncertainties with little effect: response criteria for stopping treatment different in trials/model to those used in clinical practice; pooling data for load and no- load arms may reduce some statistical uncertainty but has minor effect on modelled results

Company's model

Most model parameters (excluding relative effectiveness parameters) same as model for TA383

Decision-tree covering the initial period until BASDAI50 response assessment.

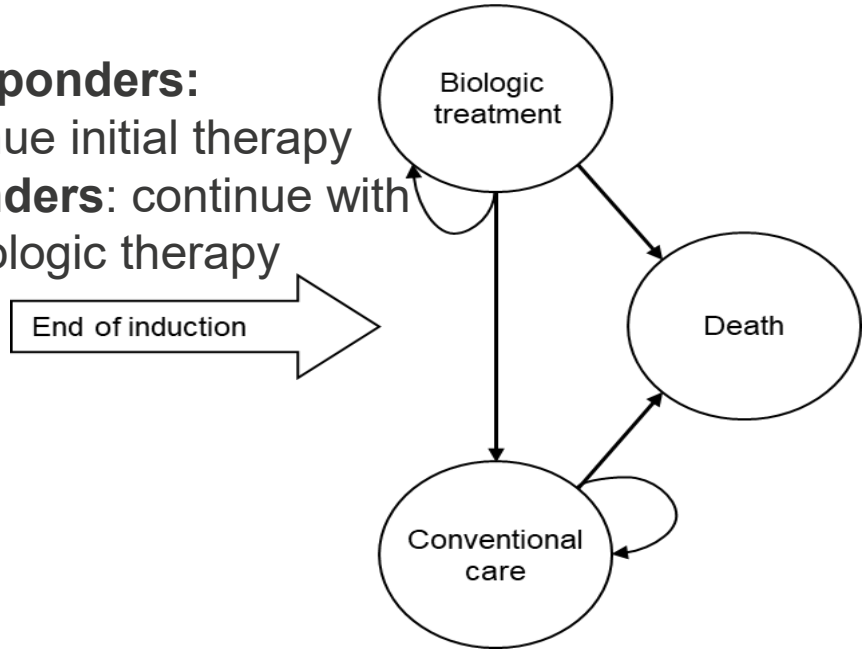


3 months of induction treatment (with a 12-week stopping rule for TNF-α inhibitors and a 16-week stopping rule for secukinumab).

Post-induction Markov model structure.

Non-responders: discontinue initial therapy

Responders: continue with same biologic therapy



Company base case, people only have 1 biological treatment then conventional care.

Company's model

Characteristics	Company model	
Intervention	150mg of secukinumab with loading dose	
Comparator	In base case analysis • conventional care (NSAIDS and physiotherapy) • TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept and golimumab individually) • TNF-α combined (based on company's estimates of market share of each inhibitor)	
Reflected population in PREVENT. Starting cohort are TNF-α naïve.	TNF-α naïve N=501	TNF-α experienced N= 54
	Mean age 39.0 years	mean age 42.8 years
	46.1% male	44.4% male
	Baseline BASDAI [redacted]	
	Baseline BASFI [redacted]	

NOTE: Company did not present a base- case analysis for sub-group of people unsuitable for treatment with TNF-α inhibitors

Changes in BASFI and BASDAI are modelled over time

- Model tracks changes in BASFI and BASDAI over time.
  - People continuing on treatment after induction assumed to have constant BASDAI.
  - BASFI progresses over time but at a reduced rate in people responding to treatment (same as TA383)
- Utility values and costs linked to BASFI and BASDAI.
  - EQ-5D-5L data collected in PREVENT at baseline and weeks 8,16,24,52.
  - Data mapped to 3L valuation set using van Hout mapping function.
  - Company developed linear-mixed model to relate EQ-5D index scores to values of BASDAI and BASFI.
  - ERG noted not consistent with non-linear model used in TA383 and used the TA383 model in its base case

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Modelling of treatment effectiveness

- Treatment is modelled to affect:
  - % who have a BASDAI 50 response (a 50% change from baseline in BASDAI score),
  - change from baseline in both BASDAI and BASFI, and,
  - long-term progression in BASFI
- The company's model uses BASDAI50 as a response criterion:
  - In TA383, although BASDAI50 used as response criterion in model, clinical experts stated less restrictive criteria used in clinical practice to define adequate response to continue treatment.
  - Continuation criteria in TA383 BASDAI50 or reduction in BASDAI by 2 or more units and a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more
- In company base-case, % of people having a BASDAI 50 response, changes in BASDAI and BASFI after induction informed by results from NMA.
- **Company**: sensitivity analysis using ASAS40 as a response criterion shows similar results to BASDAI50 and does not significantly affect cost-effectiveness.
- **ERG**: Composite criteria (NICE guidance TNF-α stopping rule) may significantly increases the proportion of responders. Implications for the level of response (change from baseline in BASDAI and BASFI scores) is unknown, but lower changes from baseline with the composite response criteria are expected.

Costs assumed for TNF-α inhibitors

- Company used 'market-share' information, averaged across months in order to cost 1)TNF-α inhibitors using a single comparator to reflect the class or 2) when the model considered subsequent TNF-α treatment.

Biologic treatment	Jan' 19	Feb' 19	Mar'19	Apr' 19	May' 19	Jun' 19	Jul' 19	Aug '19	Sep' 19	Oct' 19
SEC	[redacted]									
CER P	[redacted]									
ETN	[redacted]									
ETN BS	[redacted]									
ADA	[redacted]									
ADA BS	[redacted]									
GOL	[redacted]									

- **ERG**: company's market share data not representative of the expected use of TNF-α inhibitors in 1st line treatment in clinical practice. Recently available (late 2018) biosimilar for adalimumab is the cheapest TNF-α inhibitor and its use in the NHS is expected to keep increasing.
- Costs of 1st-line TNF-α inhibitors likely to be closer to cost of adalimumab's biosimilar.

Costs assumed for TNF-α inhibitors: technical engagement responses

Company:

- Agree adalimumab biosimilar is most widely used TNF-α inhibitor in clinical practice for nr-axSpA.
- Inappropriate to use adalimumab biosimilar cost to represent the whole class of TNF-α inhibitors given that:
  - adalimumab biosimilar <50% of prescriptions in the NHS
  - people with contraindications such as patients with moderate to severe heart failure will not receive adalimumab (caution advised in using adalimumab in people with MS) 1st-line and secukinumab offers treatment choice for these people.
  - Inappropriate to restrict access to secukinumab to 2nd line when it is cheaper than [other TNF-α] inhibitors recommended by NICE

ERG response:

- Secukinumab is slightly more costly and considerably less effective (dominated) than adalimumab biosimilar suggesting that 1st line use of secukinumab is not cost-effective (in ERG's preferred analyses).
- Exploratory analyses suggest that 2nd line use of secukinumab may be cost-effective when higher costs are assumed for the 2nd line TNF-α inhibitor (adalimumab biosimilar having already been used 1st line)
- Company has not presented evidence for secukinumab when TNF-α inhibitor treatment is contraindicated.

Modelling assumption: baseline BASDAI and BASFI scores conditional on response

Background

- Analysis of PREVENT and ABILITY (trial of adalimumab) showed relationship between response and a person's baseline BASFI and BASDAI. Company uses average ratio baseline: response observed in PREVENT + ABILITY to estimate a baseline BASFI and BASDAI for responders in the model.
- Responders modelled to have lower baseline BASFI and BASDAI than non responders
- More effective treatments (with more responders) have lower baseline BASFI/BASDAI than less effective treatments
- For a given baseline value for the overall population, conditional baselines should also change as the proportion of responders changes i.e conditional baselines will also change across NMA models.
- In TA383, the committee preferred the use of **common baselines** across responders and non-responders because
  - "Someone with more severe disease (higher baseline scores) must have larger absolute improvements than someone with less severe disease to have a BASDAI 50 response"
  - "No evidence (for TNF- α inhibitors) that people with more severe disease were less likely to have a clinically meaningful benefit than those with less severe disease".

Modelling assumption: baseline BASDAI and BASFI scores conditional on response (2)

ERG highlighted that the assumption of **conditional baselines** is supported by trial evidence from PREVENT and ABILITY-1 as shown below:

ERG considers use of conditional baselines appropriate, but an area of uncertainty

	SEC (PREVENT)	ADA (ABILITY-1)	CC (PREVENT)	average ratio (SEC + ADA)
Baseline BASDAI values for responders	[redacted]	6.21	[redacted]	
Baseline BASDAI values for non - responders	[redacted]	6.53	[redacted]	
Ratio (responder vs. non-responder)	[redacted]	0.95	[redacted]	[redacted]
Baseline BASFI values for responders	[redacted]	3.6	[redacted]	
Baseline BASFI values for non -responders	[redacted]	4.97	[redacted]	
Ratio (responder vs. non-responder)	[redacted]	0.72	[redacted]	[redacted]
Change in BASDAI for responders	[redacted]	-4.79	[redacted]	
Change in BASDAI for non-responders	[redacted]	-0.55	[redacted]	
Ratio (responder vs. non-responder)	[redacted]	8.71	[redacted]	[redacted]
Change in BASFI for responders	[redacted]	-2.75	[redacted]	
Change in BASFI for non-responders	[redacted]	-0.32	[redacted]	
Ratio (responder vs. non-responder)	[redacted]	8.59	[redacted]	[redacted]

ERG report table 15, page 69

Baseline BASDAI and BASFI scores conditional on response: technical engagement responses

Company:

- Agree with ERG that use of conditional baselines is area of uncertainty
- Agree that use of composite outcomes (NICE guidance stopping criteria) in clinical practice will affect the proportion of responders to an extent. However, likely to affect all comparator treatments, not just secukinumab. Ratio of changes from baseline for responders versus non-responders is uncertain for most anti-TNFs.

ERG response:

- The modelled response variable in the cost-effectiveness analysis is BASDAI50 and trial data shows that, under this criteria, conditional baselines are justified.
- Differences between responders and non responders in baseline BASDAI may be less likely if using the broader response criteria (NICE guidance stopping criteria) used in clinical practice as noted in the committee deliberations in TA383.
- Use of conditional baselines is a significant area of uncertainty as changing to a common baseline model has significant impact on cost-effectiveness.
- The mechanism by which cost-effectiveness changes is complex and very reliant on the magnitude of the difference between the baseline values for responders and non-responders (determined by the ratio). The main difference between the ERG base-case and analyses using common baselines depend mostly on TNF-α inhibitors which are assumed to have lower ratio values than secukinumab.

Subsequent treatments – sequence model

Background

- Company base case model does not consider subsequent treatment with biologics when considering 1st-line use of secukinumab.
- NICE recommends sequential use of TNFs (TA383); these are relevant comparators when secukinumab is positioned as a 2nd- line therapy
- A scenario analysis (sequence model) by the company compares secukinumab followed by a basket of TNF-α inhibitors with each TNF-α inhibitor followed by a basket of all other options.
- Company assumes the characteristics of patients starting 2nd-line treatment is based on the biologic-experienced subgroup in PREVENT [redacted]
- **ERG**: A reduction in treatment effectiveness for subsequent treatments based on PREVENT subgroup unreliable. Evidence based on registries in rad-axSpA such as the Dutch DANBIO registry is more suitable.
- All people initiating 2nd-line therapy are assigned the same baselines (conditioned on their response in 2nd-line) as people starting 1st line therapy. Does not account for disease progression.
- Modelling of patients' BASFI and BASDAI scores is incorrect in the sequence model and it can only be used if common baselines are considered.

Subsequent treatments – ERG sequence model

ERG's scenario treatment sequence model compares

- Secukinumab → adalimumab biosimilar→ conventional care
- Adalimumab biosimilar → etanercept biosimilar → conventional care

- Uses common baselines
- Accounts for BASFI progression over 1st line treatment
- DANBIO registry* used to estimate the 2nd line clinical effectiveness of TNF-α inhibitor

N.B. ERG preferred to use the non-sequence model with conditional baselines because the direction of bias of not incorporating subsequent treatments was easier to predict

* Glintborg B et al. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor α inhibitor therapy: results from the Danish nationwide DANBIO registry. *Ann Rheum Dis* 2013;**72**:1149-55.

ERG base-case for 2nd line use of secukinumab

- Uses the company's non-sequence model
- Base line BASFI scores reflect non-responders to TNF-α inhibitors baseline BASFI (i.e. 5.537) inflated by the expected BASFI progression during 1st line treatment
- Treatment effect based on data from DANBIO registry rather than PREVENT TNF-α inhibitor experienced subgroup
- Costs for TNF-α inhibitor was based on etanercept used 2nd line (assumed adalimumab would have been used as the first TNF-α inhibitor)

2nd line biological treatment: responses to technical engagement

Company:

- Agree that people are likely to receive TNF-α inhibitors after 1st-line use of secukinumab, after discussion with clinician and considering costs if more than one treatment is suitable.
- TNF-α inhibitors are relevant comparators for 2nd-line use of secukinumab. However, no randomised data available to inform cost-effectiveness estimates.
- Availability of RCT data provides more robust evidence than the DANBIO registry, which did not have a control arm to inform relative efficacy. The registry is also not based in the UK, so may not be generalisable to clinical practice.

- **ERG response**:

Sequence model

- In the ERG's sequence model, subsequent treatments have a significant impact on cost-effectiveness estimates.
- If secukinumab is used 1st line, adalimumab (lowest cost TNF-α inhibitor) would be used after; this would be compared with adalimumab followed by etanercept

Modelling second line treatments

- Due to insufficient data, 2nd-line (and subsequent) use both TNF-α inhibitors and secukinumab is uncertain.
- Estimates from the DANBIO registry are more reliable than results from a small subgroup from PREVENT and relate to reductions in effectiveness for 2nd and 3rd line treatment in relation to 1st line treatment using relative risks.

Cost effectiveness results

Some of the TNF-α inhibitors are available at a reduced price to the NHS, negotiated via the NHS Commercial Medicines Unit. Results incorporating these prices will be presented in Part 2

Company base-case results (load arm only)

Secukinumab is less costly and less effective than the TNF-α inhibitors

1st-line use of secukinumab using conditional baselines

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER incremental (£/QALY)
Conventional care	[redacted]	[redacted]	–	–	–
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
Adalimumab biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£5,445
Etanercept biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	£157,868
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	£572,694
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

1st-line use of secukinumab compared to a single TNF-α inhibitor using conditional baselines + market share for TNF-α inhibitor drug costs

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (fully incremental)
Conventional care	[redacted]	[redacted]	-	-	-
SEC	[redacted]	[redacted]	[redacted]	[redacted]	£7,460
TNFi	[redacted]	[redacted]	[redacted]	[redacted]	£23,667

ERG base case

- Secukinumab less effective and less costly than TNF-α inhibitors, fewer cost savings than company base case.
- ERG note no evidence submitted by company for people for whom a TNF-α inhibitor is unsuitable and for whom conventional care is the valid comparator
- ERG do not consider ICER secukinumab vs. conventional care (£8,399), based on data for whole population has not been shown to be valid for subgroup of people for whom a TNF-α inhibitor is unsuitable

	Incremental (sec vs. TNFi)	
	costs	QALYs
Company base case	XXXXX	XXXX
1. CS base-case, correcting model errors	XXXXX	XXXX
2. 1 + Costing TNFi based on adalimumab biosimilar price (cheapest TNFi)	XXXXX	XXXX
3. 2 + Baseline BASDAI and BASFI values based on EuroSpA and change values for placebo based on pooling across relevant trials	XXXXX	XXXX
4. 3 + pooled secukinumab arms of PREVENT	XXXXX	XXXX
4 + York utility algorithm (ERG's PREFERED BASE-CASE	XXXXX	XXXX

Incremental costs and QALYs and ICER vs. conventional care calculated by NICE from ERG report table 25

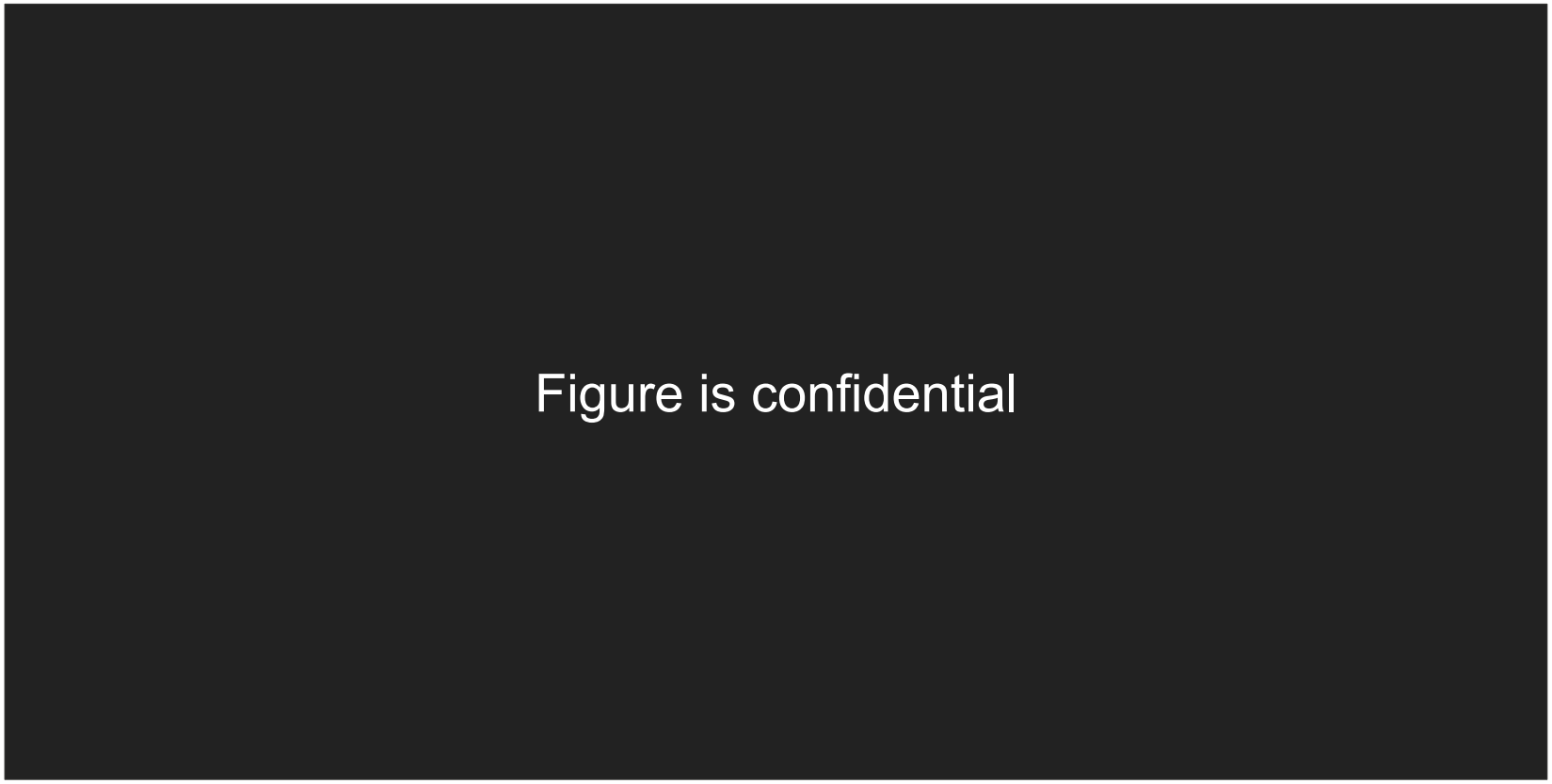
Sensitivity analyses on ERG's base case (1st-line use using non- sequence model)

N.B. where the ERG reports an ICER for TNFi, this is the extra costs for TNFi vs SEC/ extra QALYs for TNFi vs. SEC

Analysis	Discounted costs			Discounted QALYs			
	SEC →CC	TNFi →CC	CC	SEC →CC	TNFi→CC	CC	ICER (SEC→ CC vs TNFi→ CC)
ERG's base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,673 (for TNFi)
7. Common BASDAI & BASFI baselines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TNFi dominates
8.Using no-load costs for SEC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,700 (for TNFi)
9.No BASFI progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,286 (for TNFi)
10.Company's market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,811 (for TNFi)

ERG's scenarios around its base case vs TNFi

In all scenarios secukinumab gives fewer QALYs than TNFi; secukinumab is more costly and less effective than TNFi (dominated) if common baselines used



ERG treatment sequence scenario with common baselines

	SEC→ TNFi→ CC	TNFi→ TNFi→ CC	CC	SEC→ TNFi→ CC	TNFi→ TNFi → CC	CC	ICER (TNFi→TNFi→ CC Vs SEC→TNFi-→CC)
Treatment sequence with common baselines. Note that 2nd TNFi is costed as etanercept biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,102 (for TNFi sequence

Secukinumab →TNF→ CC [redacted] compared with TNFi→TNFi→CC

Sensitivity analyses on ERG's base case (2nd-line use)

Analysis	Discounted costs			Discounted QALYs			ICER (1st line use of SEC)
	TNFi-> TNFi->CC	TNF-> SEC->CC	CC	TNFi-> TNFi-> CC	TNFi-> SEC-> CC	CC	ICER(TNFi->SEC-> CC vs TNFi >TNFi-> CC)
ERG's base-case for 2nd line use of secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Lower overall BASFI baseline (i.e. 5.948 - 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,362 (for TNFi)
Higher overall BASFI baseline (i.e. 5.948 +1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,799 (for TNFi)
Common baselines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,466 (for TNFi)
Costing 2nd lines TNFi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
the most expensive TNFi (i.e. GOL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,508 (for TNFi)
on company's market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,509 (for TNFi)
ADA BS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TNFi dominates
Reduction effectiveness based on PREVENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,883 (for TNFi)

TNF→SEC→ CC vs. TNFi→TNFi→CC [redacted] QALYs; ICER vs. CC £19,421 (for overall trial population, not for subgroup who cannot have TNF-α inhibitors)

Key issues (cost-effectiveness)

1 Costs assumed for TNF-α inhibitors : major impact on cost effectiveness

- As costs for TNF-α inhibitors are the key driver of cost effectiveness analyses, should the least expensive nationally available TNF-α inhibitor (adalimumab biosimilar) be used to represent the class at 1st line OR
- Should the company's approach of using market share of TNF-α inhibitors be used?

2 Conditional baselines: area of uncertainty

- Whether baseline BASDAI and BASFI response should be conditional on response is an area of uncertainty which significantly impacts cost-effectiveness estimates. Both company and ERG prefer conditional baselines but the committee for TA383 preferred the use of a common baselines. What is the committee's preference for this appraisal?

3 Subsequent treatments : area of uncertainty and relates to 2

- Company base case model does not consider subsequent treatment with biologics when considering 1st-line use of secukinumab. However, modelling of patients' BASFI and BASDAI scores is incorrect in sequence model and it can only be used if common baselines are considered. ERG base-case uses the non-sequence model with conditional baselines. Which approach is appropriate for decision-making?
- Additional uncertainties with little effect: response criteria for stopping treatment different in trials/model to those used in clinical practice; pooling data for load and no- load arms may reduce some statistical uncertainty but has minor effect on modelled results