Nemolizumab for treating prurigo nodularis [ID6451]

For screen – confidential information redacted

Technology appraisal committee B [5 March 2025]

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Nemolizumab for treating prurigo nodularis

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on prurigo nodularis

Chronic neuroimmune dermatological disease causing intense, chronic itching

Causes

- Rare, chronic, neuroimmune dermatological disease
- Associated with IL-31 driven neuroimmune responses

Epidemiology

- Estimated prevalence in England is 3.27 per 10,000 people
- Approximately 70% of patients present at the age of 50 years or older

Diagnosis and classification

- Characterised by multiple hyperkeratotic nodules and papules typically distributed symmetrically along person's trunk and extremities – extremely itchy

Symptoms and prognosis

- Symptoms can include a combination of itching, pain, burning and stinging sensations
- Intense, chronic itching causes bleeding and impacts sleep, leading to psychological effects including depression, and impaired quality of life

NICE

Abbreviations: IL-31, interleukin-31

Patient perspectives

Devastating, life-changing disease

Submissions from Prurigo Nodularis International and patient experts

- There is little physical, mental and emotional peace as the itch is constant
- Detrimental impact on all aspects of life, including physical, mental, emotional, financial and relationships
- Time consuming and expensive applying moisturisers and other creams
- Shame and social stigma attached to the disease
- Disease often spreads to cover a lot of the body
- People are at risk of developing other conditions because of long-term inflammation
- No targeted treatments and current treatments often do little to nothing to help treat condition, but can have serious side-effects, or can lead to people developing other conditions
- Nemolizumab could help to relieve itch, flatten nodules and has few side effects

"The disease influences what I wear, what I eat, where I go, who I see, in effect, there is no aspect of my life that the disease has not controlled or impacted. The disease has destroyed my life as it was."

Patient descriptions of PN:
"Depressing and hopeless"
"Totally debilitating"
"Never-ending, incurable and miserable"

"[Nemolizumab] saved my life … no itch & lesions healed"

Clinical perspectives

Significant unmet clinical need for a safe and effective treatment for PN

Submission from British Association of Dermatologists (BAD)

- Condition is currently treated in primary care, then in secondary care where disease is unresponsive, severe, or people request a referral or cannot access medication within primary care
- There is a general consensus to start treatment with topical therapy, then phototherapy, then progress to systemics and biologics, with additional medicines like antihistamines or antidepressants as required
- Most important outcomes are peak pruritic numerical rating scale (PPNRS), visual analogue itch scales (VAS), PN investigators global assessment (IGA) responses, improvement in quality of life and sleep, reduction in skin manifestations
- Nemolizumab is likely to be used for people with severe/recalcitrant disease when topical anti-inflammatory/phototherapy and at least 1 systemic anti-inflammatory medication has been ineffective or contraindicated
- The BAD is currently developing a clinical guideline on managing PN, which is likely to be published this year

Abbreviations: PN, prurigo nodularis; BAD, British Association of Dermatologists

Equality considerations

Are there any equality issues to consider?

Race

- Evidence from the US suggests a higher prevalence of prurigo nodularis in people of Black African, Black Caribbean, Hispanic, South Asian and East Asian ethnicity
    - However, an NHS dataset* indicated that 82.8% of patients with PN were of white background which is in alignment with the UK 2021 census.
- Erythema may be underestimated in those with darker skin tones, so the severity assessment of their skin disease may be underestimated.
- Patients with skin of colour have a greater propensity for papulation, lichenification, PN, pigmentary changes, and extensor surface involvement than patients with white skin

*https://pubmed.ncbi.nlm.nih.gov/35083742/)

Sex

- PN may be more common in women (60% female in OLYMPIA trials)

Disability

- Assessment of itch severity, sleep quality and quality of life may be more difficult in people with visual, hearing or cognitive impairment or communication difficulties
    - NICE comment: challenges highlighted are not limited to this disease area.

Other (professional organisation submission)

- Quality of life measures such as DLQI (used in OLYMPIA trials) may not adequately capture impact in older people or those who are not in a relationship. It is also known to capture anxiety and depression poorly across all groups (two parameters that are commonly negatively influenced by NP).

Abbreviations: PN, prurigo nodularis

Treatment pathway*

Treatments all used off-label to relieve symptoms

IFSI stepwise treatment recommendations

- Use emollients in every step
- Interdisciplinary approach e.g. if suspected psychological factors
- Individualised – therapies can be combined, steps skipped

STEP 4

- NK1R antagonist
- μ-opioid receptor antagonists
- Dupilumab (TA955: not recommended)
- Nemolizumab
- Thalidomide in exceptional cases

STEP 3

- Gabapentin, pregabalin
- Antidepressants
- Cyclosporin
- Methotrexate

STEP 2

- Topical capsaicin
- Intralesional corticosteroids
- UV therapy

STEP 1

- Topical corticosteroids
- Topical calcineurin inhibitors
- H1-antihistamines

Company's comparators are based on discussion with experts:

- BSC is emollients, TCSs and TCIs.
- Antihistamines, systemic corticosteroids and immunosuppressants (methotrexate and ciclosporin) are also used.

Are the company's comparators appropriate?

Abbreviations: IFSI, International Forum for the Study of Itch; NK1R, neurokinin-1 receptor; BSC, best supportive care; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors; UV, ultraviolet; BSC, best supportive care

*see link to Decision problem

Nemolizumab (Nemluvio, Galderma)

Marketing authorisation	UK MA granted Feb 2025: Nemolizumab is indicated for the treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy
Mechanism of action	• Humanised monoclonal antibody, targeting the interleukin-31 receptor alpha. • Interleukin-31 is a key mediator of itch
Administration	Subcutaneous injection – self-administered • < 90 kg: 30 mg every 4 weeks • ≥ 90 kg: 2 x 30 mg every 4 weeks

Price	• [redacted] for 30 mg dose
	• Cost for a year of treatment:
	  • < 90 kg: [redacted]
	  • ≥ 90 kg: [redacted]
	• Simple patient access scheme in place

Abbreviations: MA, marketing authorisation

Key issues

Issue	ICER impact
Comparators: • Are the company's comparators appropriate?	Unknown
Stopping rule: • How would a stopping rule likely be implemented in clinical practice?	Unknown
Costs: • Should costs of best supportive care be included in the model without benefits?	Small
Utilities: • Should baseline utility values or trial observed utility values be used for non-response state? • Should the model include a partial response for non-responders in the nemolizumab arm? • Should the model include a 5% utility weight increase for responders?	Large

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Clinical trial designs*

Company presented evidence from two phase 3 clinical trials and a long-term extension (LTE) study – data from all used in economic model

	OLYMPIA 1 (N=286)	OLYMPIA 2 (N=274)	OLYMPIA LTE (N=508)
Design	Phase 3, multicentre, double-blind, placebo-controlled, randomised	Phase 3, multicentre, double-blind, placebo-controlled, randomised	Phase 3 prospective long-term extension study
Duration	24 weeks	16 weeks	196 weeks
Intervention	< 90 kg at baseline: 60 mg loading dose, then 30 mg at weeks 4, 8, 12, 16 and 20. ≥ 90kg at baseline: 60 mg loading dose, then 60 mg at weeks 4, 8, 12, 16 and 20.	< 90 kg at baseline: 60 mg loading dose, then 30 mg at weeks 4, 8, 12 and 16. ≥ 90kg at baseline: 60 mg loading dose, then 60 mg at weeks 4, 8, 12 and 16.	< 90 kg at baseline: 30 mg every 4 weeks. ≥ 90kg at baseline: 60 mg every 4 weeks.
Population	Adults with PN, at least 20 nodules, IGA score ≥ 3, PP NRS score ≥ 7.0. No specification of prior treatments included.	Adults with PN, at least 20 lesions, IGA score ≥ 3, PP NRS score ≥ 7.0. No specification of prior treatments included.	Adults previously enrolled in OLYMPIA 1 or 2 or Phase 2a study

Abbreviations: IGA, Investigator's Global Assessment; PP NRS, peak pruritis numerical rating scale; PN, prurigo nodularis

EAG noted an additional phase 2 trial that could have been included (NCT03181503) but agrees it would make little difference to the results used in the economic modelling.

*see link to BSC treatment basket

Clinical trial results

Significantly more in nemolizumab arm had a reported improvement in PP NRS and IGA scores

		OLYMPIA 1 (N=286)		OLYMPIA 2 (N=274)	
Outcome		Nemolizumab	Placebo	Nemolizumab	Placebo
PP NRS improvement ≥4 points from baseline	Wk 16	58.4%	16.7%	56.3%	20.9%
	Wk 24	[redacted]	[redacted]	N/A	N/A
IGA* success (change of ≥2-points from baseline and score of 0/1)	Wk 16	26.3%	7.3%	37.7%	11.0%
	Wk 24	[redacted]	[redacted]	N/A	N/A

*IGA is a measure of the number of nodules:
- IGA of 3 = moderate disease
- IGA of 4 = severe disease

In the economic model, pooled week 16 data from OLYMPIA 1 & 2 used:

Week 16 data pooled from OLYMPIA 1 and 2	Nemo arm	BSC arm
Percentage achieving composite response outcome: • ≥ 4 PP NRS, and • IGA score 0 or 1 + improvement ≥2 pts	[redacted]	[redacted]

Abbreviations: IGA, Investigator's Global Assessment; PP NRS, peak pruritis numerical rating scale; PN, prurigo nodularis; NMA, network meta-analysis

EAG comments
- Company excluded comparators not approved for clinical practice in the UK
- Comparing nemolizumab against these could have been valuable
- An NMA with around 5 other comparators could have been done, although the available evidence would limit usefulness

Stopping rule

Consideration included in SPC as to stopping treatment after 16 weeks of no response

Company

- Stopping rule included in Summary of Product Characteristics (SPC):

> Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment for prurigo nodularis.

- Economic model assumes patients discontinue treatment if not reached a response after 16 weeks, or once a composite response has been lost
- Composite response in the model
  - Itch improvement ≥ 4 PP NRS
  - IGA score 0 or 1 + improvement ≥2 pts

EAG comments

- Clinical expert suggested people may wish to continue treatment with nemolizumab if it is improving symptoms, even if composite response level not reached
- Would prefer a partial response health state in the economic model, with people remaining on treatment with some quality-of-life benefits

NB. No stopping rule considered in TA955

How would a stopping rule likely be implemented in clinical practice?

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Abbreviations: IGA, Investigator's Global Assessment; PP NRS, peak pruritis numerical rating scale

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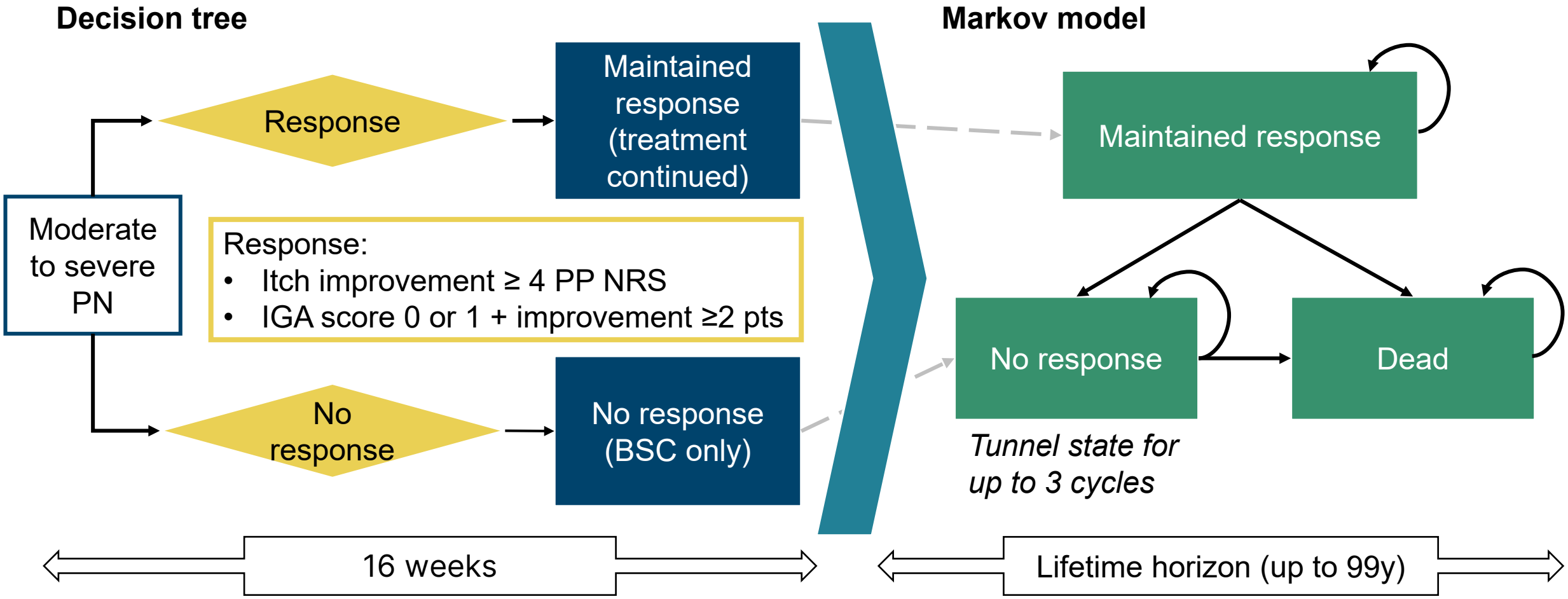
Model structure

Two-stage model

Company's model includes decision tree for 16 weeks, followed by a Markov cohort model with 3 health states



Abbreviations: PN, prurigo nodularis; BSC, best supportive care; PP NRS, peak pruritus numerical rating scale; IGA, Investigators global assessment

Model overview

Intervention

- Nemolizumab with best supportive care
- Dose dependent on patient weight, proportions based on OLYMPIA 1&2
  - 30% assumed to be ≥ 90 kg
  - 70% assumed to be < 90 kg

Comparator (see also BSC treatment basket)

- Best supportive care, defined as topical emollients, TCSs, TCIs, antihistamines, systemic corticosteroids and immunosuppressants
- Assumed that responders on active treatment have fewer BSC treatments than non-responders in both arms

Response (see also Response rates in the model)

- Composite response in company base case:
  - Itch improvement ≥ 4 PP NRS, **and**
  - IGA score 0 or 1 + improvement ≥2 points
- Based on OLYMPIA 1&2 data at week 16
- Calculated as [redacted] in the nemolizumab arm and [redacted] in the BSC arm
- Company scenario analysis using PP NRS alone

Treatment discontinuation and waning (see also Treatment discontinuation and Treatment effect waning)

- Discontinuation rates applied in both arms
- A treatment waning effect is also applied based on TA955

EAG comments

- Note CPRD/HES dataset suggested patients in practice would be older and heavier than in OLYMPIA trials
- Patient weight doesn't change over time in model
- Proportion >90kg not in PSA – EAG adds this
- Composite response is a high bar to reach in 16 weeks – could lead to a conservative estimate of treatment effect in both arms
- EAG would prefer alternate BSC costs, e.g. including wastage (NB. BSC costs are removed in current EAG base case – see next slide)
- Treatment discontinuation and treatment effect waning are not key drivers of cost-effectiveness, but the parameter values are highly uncertain

Abbreviations: BSC, best supportive care; PP NRS; peak pruritic numerical rating scale; IGA, investigators' global assessment; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors' CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; PSA, probabilistic sensitivity analysis

Key Issue: Modelling of best supportive care

Small ICER impact

Model includes costs but not benefits of BSC after "no response"

Background

- Markov model does not allow for possibility of a response to be regained after it is lost in either arm
- BSC treatment basket in non-response state is more intensive than in induction phase or for response state – 77% receive methotrexate and 15% oral prednisolone
  - Treatment costs incurred indefinitely for full model duration with no benefit

Company

- Existing treatments target symptoms not underlying disease
- 28% of patients in a European study considered no treatments effective
- Lack of clinical information to support changing model structure to allow a response to be regained once it is lost

EAG comments

- In practice, treatments unlikely to be continued indefinitely without benefit
- Company's model predicts that patients spend longer in non-response state if they were initially in BSC arm compared with nemolizumab arm
- Would prefer addition of a partial response health state – achieving composite response is a high bar and possible to get some benefit of treatment without reaching the definition of composite response
- Aware of 2 studies that qualitatively suggest possible benefit from immunosuppressants for PN (identified in TA534; dupilumab for moderate to severe AD)

→ EAG base case removes costs of BSC in non-response state due to lack of data

Should costs of best supportive care be included in the model without benefits?

Abbreviations: AD; atopic dermatitis, BSC, best supportive care; PN, prurigo nodularis

Key issue: Utilities [1]*

Large ICER impact

Company

- Health state utility values based on EQ-5D-3L data pooled across OLYMPIA 1 and 2 trials at baseline and 16 weeks

Responders

- Up to year 1, utility based on week 16 mean utility score of all responders observed in the trials, independent of treatment arm (0.922)
- Beyond year 1, utility is increased by 5% for the remainder of time in the response state
  - Based on data from long-term extension study of nemolizumab in atopic dermatitis, clinical advice and statistical analysis

Non-responders

- Return to mean baseline utility observed across all participants
- However, for non-responders in nemolizumab arm, utility value assumed is the mid-point of baseline and responder values, to account for potential partial treatment response (in line with TA955) – applied from weeks 8 to 52 in cycle 1, or for a full 52-week cycle for those who discontinue or lose a response to nemolizumab after cycle 1

Parameter	Company	EAG	
Baseline (wk0-8)	0.579	0.579	
Responders			
Responder y1 (Week 9–52)	0.922	0.922	
Responder y2	0.968	0.922	3
Responder y3+	0.968	0.922	
Non-responder			
Non-responder y1	Nemo: 0.751 BSC: 0.579	0.734	2
Non-responder y2	0.579	0.734	1
Non-responder y3+	0.579	0.734	

Abbreviations: EuroQol 5-dimension 5-level version; BSC, best supportive care

*see also Utility values in TA955

Key issue: Utilities [2]

Large ICER impact

EAG comments

1 **Use of baseline utility values in non-response health state**

- For response states, company has used observed utility data, but for non-response states, has used baseline value (0.579)
- Company could have used the pooled non-response utility value observed in OLYMPIA (0.734)
- Company cite committee preference in TA955 that non-responders would return to baseline utility at 6 months, also protocol-driven effects where participants return to a worse health state post-trial
- EAG note difference between utility value for responders and non-responders is the **most important driver** of cost-effectiveness results
- Utility value at baseline might not be generalisable to PN patients receiving BSC in clinical practice
  - Trial participants could not have some treatments in the weeks before trial entry e.g. immunosuppressants, TCIs, systemic corticosteroids
  - So, baseline utility may be reflective of PN population not receiving usual BSC treatment
- Many BSC treatments may have poor effectiveness but likely to provide some symptomatic relief
- Protocol-driven effects would likely apply to both arms, but only applied to BSC arm

→ EAG base case uses utility value observed in trial for non-response in both arms (0.734)

Should the model include a 5% utility weight increase for responders?
Should the model include a partial response for non-responders in the nemolizumab arm?
Should baseline utility values or trial observed utility values be used for non-response state?

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Abbreviations: PN, prurigo nodularis; BSC, best supportive care; TCIs, topical calcineurin inhibitors

Key issue: Utilities [3]

Large ICER impact

EAG comments

Three key points that have been explored in EAG preferred base case

2 Partial response in non-response state for nemolizumab arm only

- Lack of evidence to support a treatment-specific benefit
- Company could have built a partial response state into the model
- EAG prefers to use observed index utility scores where possible and to be consistent across treatment arms
- There does appear to be a difference in observed utility scores for non-responders at 16 weeks between treatment arms, but the magnitude is less than company's modelling

→ EAG base case removes benefit for nemolizumab arm

→ EAG scenario analysis applies a smaller benefit in first cycle only – lack of evidence beyond week 24 (cycle length is 1 year so increases uncertainty)

3 5% utility weight increase for responders

- Secondary healing of lesions could improve quality-of-life, but is unclear by how much
- Long-term data from the atopic dermatitis study, with different definitions of response, are unlikely to be transferable to PN
- Utility value at 16 weeks for responders is higher than age- and sex-adjusted general population utility norms for the UK, so increasing it further lacks face validity
- Company's regression model has major limitations regarding data availability, model specification, internal validity and face validity of utility extrapolations

→ EAG base case removes 5% utility increase

Abbreviations: PN, prurigo nodularis

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case	Slide
Best supportive care costs in non-response state	Includes additional costs of BSC in both model arms but assumes no treatment benefit	Remove all BSC costs from the non-response state of the model	17
Utility values for non-response health state	Equal to baseline utility value	Non-responder utility from trial data (issue 2)	18-20
Utility value for nemolizumab non-responders	Assigned utility value equal to the average of baseline and responder for one year following a loss of response. (BSC non-responders are assigned the non-response utility value)	Assume all non-responders are treated equally in the model and assigned the non-response utility value (issue 3)	18-20
Utility values for response health state	After year 1, 5% increase in utility (from 0.922 to 0.968) for the full duration of response	Remove 5% increase (utility remains at 0.922) (issue 1)	18-20
Adverse event disutilities	Excluded	Included – see back-up slide	36

Abbreviations: BSC, best supportive care

Company base case results

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	XXX	XXX	-	-	-
Nemolizumab + BSC	XXX	XXX	XXX	XXX	£34,523

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Nemolizumab + BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,655

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Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

Company's deterministic scenario analyses

No.	Scenario (applied to company base case)	Inc costs (£) versus BSC	Inc QALYs versus BSC	ICER (£/QALY) versus BSC
1	**Company base case**	[redacted]	[redacted]	£34,523
2	Response defined as PP NRS ≥4	[redacted]	[redacted]	£35,120
3	Include indirect costs	[redacted]	[redacted]	£24,699
4	Include adverse event disutilities	[redacted]	[redacted]	£34,538
5	Exclude treatment waning effect	[redacted]	[redacted]	£37,054
6a	All receive 60mg Q4W maintenance	[redacted]	[redacted]	£54,867
6b	All receive 30mg Q4W maintenance	[redacted]	[redacted]	£25,804
7	Remove excess mortality for PN	[redacted]	[redacted]	£34,475
8a	Response defined at week 24 (OLYMPIA 1)	[redacted]	[redacted]	£37,231
8b	Response defined at week 24 (OLYMPIA 1)/ week 16 (OLYMPIA 2)	[redacted]	[redacted]	£36,731
9	HSUV capped at general population norms with decrements applied to all health states	[redacted]	[redacted]	£34,523
10a	Remove BSC treatment discontinuation	[redacted]	[redacted]	£34,647
10b	BSC treatment discontinuation from OLYMPIA 1, placebo arm, week 24	[redacted]	[redacted]	£34,400

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PN, prurigo nodularis; PN NRS, peak pruritic numerical rating scale; Q4W, 4-weekly; HSUV, health state utility value

EAG preferred model assumptions

Changes from company base case to EAG preferred base case

No.	Deterministic scenario (applied to company base case) (individual additive scenarios)	Inc. costs (£) versus BSC	Inc. QALYs versus BSC	ICER (£/QALY) versus BSC
1	**Company base case (corrected)**	[redacted]	[redacted]	**£34,657**
2	Use a non-responder HSUV (0.734) obtained directly from the OLYMPIA trial data	[redacted]	[redacted]	£42,068
3	Remove nemolizumab partial response utility from the non-response state	[redacted]	[redacted]	£41,495
4	Remove the 5% increase in response HSUV beyond OLYMPIA trial data EQ-5D	[redacted]	[redacted]	£38,064
5	Include AE disutility	[redacted]	[redacted]	£34,672
6	Remove all BSC costs from the non-response state of the model	[redacted]	[redacted]	£37,038
7	**1-6: EAG preferred base case**	[redacted]	[redacted]	**£90,712**

Abbreviations: EQ-5D, EuroQol 5-dimension; BSC, best supportive care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; HSUV, health state utility value; AE, adverse event

EAG base case results

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	XXX	XXX			
Nemolizumab + BSC	XXX	XXX	XXX	XXX	£90,712

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	XXX	XXX			
Nemolizumab + BSC	XXX	XXX	XXX	XXX	£89,990

EAG comments: Proportion of patients weighing greater than 90kg (30% in company base case) has a large impact upon the cost effectiveness results but was not included in the company's probabilistic sensitivity analysis (PSA). EAG has added to its PSA. See also slide 34 and 35.

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

EAG deterministic scenario analyses – utility values*

EAG scenarios applied to company base case

No.	Deterministic scenario (applied to company base case)	ICER (£/QALY) versus BSC
1	**Company base case (corrected)**	**£34,657**
2	Baseline utility = 0.734 (non-responder (NR) utility at week 16)	£58,885
3	Baseline utility = 0.664 (BSC NR utility at week 16)	£44,755
4	Nemolizumab NR year 1 utility (Baseline+0.101) not applied to BSC year 1	£37,175
5	Remove NR utility benefit in year 1	£41,495
6	Remove the 5% increase in response HSUV beyond OLYMPIA trial data EQ-5D *(in EAG base case)*	£38,064
7	6 + 2	£69,446
8	6 + 3	£50,604
9	NR year 1: Nemolizumab: 0.774 for intervention from week 9-24. BSC: 0.673 from week 9-24. Weighted average of both 0.734 for the rest of the year.	£40,040
10	6 + 9	£44,658
11	6 + 3 + 9	£57,489

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NR, non-responder; EQ-5d, EuroQol 5-dimension

*see also Further EAG scenario analyses

EAG deterministic scenario analyses

Additional scenario analyses applied to EAG base case

No	Deterministic scenario (applied to EAG base case)	Inc. costs vs BSC	Inc. QALYs vs BSC	ICER (£/QALY) vs BSC
1	**EAG base case**	[redacted]	[redacted]	**£90,712**
2	Strata adjusted effect size from: A) OLYMPIA 1 alone	[redacted]	[redacted]	£98,078
3	Strata adjusted effect size from: B) OLYMPIA 2 alone	[redacted]	[redacted]	£88,080
4	Strata adjusted effect size from: all 3 nemolizumab studies	[redacted]	[redacted]	£90,978
5	Nemolizumab discontinuation = [redacted], Total who discontinued from the LTE study)	[redacted]	[redacted]	£101,206
6	Nemolizumab discontinuation = [redacted]), Total randomised for OLYMPIA with response that discontinued from LTE)	[redacted]	[redacted]	£91,648
7	Remove BSC discontinuation	[redacted]	[redacted]	£91,074

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Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; LTE, long-term extension; NR, non-responder

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Key issues

Issue	ICER impact	Slide
Comparators: • Are the company's comparators appropriate?	Unknown	7
Stopping rule: • How would a stopping rule likely be implemented in clinical practice?	Unknown	13
Costs: • Should costs of best supportive care be included in the model without benefits?	Small	17
Utilities: • Should baseline utility values or trial observed utility values be used for non-response state? • Should the model include a partial response for non-responders in the nemolizumab arm? • Should the model include a 5% utility weight increase for responders?	Large	18-20

Nemolizumab for treating prurigo nodularis

Supplementary appendix

NICE National Institute for Health and Care Excellence

Decision problem [1]

	Final scope	Company	EAG comments
Population	Adults with PN	Adults with moderate to severe PN – this is the trial population and now the expected MA wording	EAG clinical expert agrees that this is the population that is most likely to receive nemolizumab in the UK.
Intervention	Nemolizumab	Nemolizumab with BSC – anticipated use in clinical practice, validated by experts	No issues

Abbreviations: PN, prurigo nodularis; MA, marketing authorisation; BSC, best supportive care

Decision problem [2]

Link back to Treatment pathway

	Final scope	Company	EAG comments
Comparators	Established clinical management, including topical emollients, TCS, TCI, antihistamines, oral corticosteroids, phototherapy, immunosuppressive therapies (azathioprine, ciclosporin, methotrexate, or thalidomide) and antidepressants including SSRIs and SNRIs	Doesn't include phototherapy or antidepressants as not highlighted by clinicians as current treatment.	No issues
Outcomes	• Measures of disease severity • Measures of symptom control including improvement in itch • Time to relapse/prevention of relapse • Adverse effects of treatment • HRQoL • Disease-free period/maintenance of remission	Excludes disease-free period/maintenance of remission and time to relapse/prevention of relapse: not considered in TA955. Limited data for these outcomes.	EAG clinical expert's opinion, that these outcomes are relevant to PN. EAG would have welcomed a comparative analysis of off-treatment patients with those who continued to receive nemolizumab in the long-term follow-up studies.

Abbreviations: TSC, topical corticosteroids; TCI, topical calcineurin inhibitors; SSRI, selectic serotonin reuptake inhibitors; SNRI, erotonin norepinephrine reuptake inhibitors; PN, prurigo nodularis; HRQoL, health-related quality of life

Clinical trial baseline characteristics

	OLYMPIA 1		OLYMPIA 2		LTE study
	Nemo (N=190)	Placebo (N=96)	Nemo (N=183)	Placebo (N=91)	Nemo (N=508)
Male, n (%)	80 (42.1)	40 (41.7)	70 (38.3)	36 (39.6)	[redacted]
Female, n (%)	110 (57.9)	56 (58.3)	113 (61.7)	55 (60.4)	[redacted]
Age, years, Mean (SD)	57.5 (12.8)	57.6 (13.4)	53.7 (14.4)	50.8 (15.0)	[redacted]
Mean weight at baseline, kg (SD)	87.1 (21.8)	80.8 (17.8)	79.7 (17.8)	80.8 (22.3)	[redacted]
Mean BMI, kg/m^2 (SD)	30.0 (6.5)	28.2 (5.2)	28.2 (5.3)	28.5 (5.9)	[redacted]
Mean baseline height, cm (SD)	170.0 (9.5)	168.9 (9.9)	167.9 (8.5)	167.7 (10.8)	[redacted]
Race					
White	160 (84.2)	81 (84.4)	147 (80.3)	68 (74.7)	[redacted]
Black or African America	18 (9.5)	10 (10.4)	5 (2.7)	7 (7.7)	[redacted]
Asian	10 (5.3)	2 (2.1)	23 (12.6)	14 (15.4)	[redacted]
American Indian or Alaska native	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]
Other	1 (0.5)	2 (2.1)	5 (2.7)	2 (2.2)	[redacted]
Not reported	0 (0.0)	1 (1.0)	1 (0.5)	0	[redacted]
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]
Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	[redacted]

Abbreviations: SD, standard deviation; BMI, body mass index

Subgroup analysis

By weight at randomisation

Forest plot of proportion of patients with an improvement >4 from baseline in weekly average PP NRS at week 16 – OLYMPIA 1 and 2 ITT population

Forest plot of proportion of patients with an IGA success at week 16 – OLYMPIA 1 and 2 ITT population

Abbreviations: PP NRS, peak pruritis numerical rating scale; IGA, investigators global assessment; ITT, intention to treat; CI, confidence intervals

Link back to EAG base case results

Population in the model

EAG identified a study suggesting people eligible for nemolizumab in UK clinical practice may be older and of higher weight than modelled population

Characteristic	Company modelled population based on OLYMPIA1 & 2 pooled datasets	Bahloul et al, 2023, CPRD data for England
Sample	N=560 Adults with moderate to severe PN	N=2,462 Adults with moderate to severe PN
Age (mean, years)	55	61
Gender (proportion female)	60%	63%
Weight (mean, kg)	82.56	NR, but calculated by EAG as 86.25 based on reported BMI = 31kg/m2 and UK age and gender adjusted population height: (175cm x 37%) + (162cm x 63%) = 1.668m obtained from Health survey for England data 2021.

Abbreviations: PN, prurigo nodularis

Issue: Adverse event disutilities

Small ICER impact

Company

- Base case doesn't include adverse event (AE) disutilities because:
  - impact of AEs on quality of life already captured in EQ-5D health state utility values
  - clinical expert suggested most AEs would be resolved in 2 weeks
  - approach accepted in TA955
- Scenario provided where AE disutility is applied, for AEs occurring in at least 2% of participants in OLYMPIA 1&2

EAG comments

- EAG considers there is lack of evidence to suggest the EQ-5D index scores are impacted by adverse events
- Given the assumed short duration of AEs in the company's model, unless all EQ-5D utilities were collected at the exact time an adverse event was occurring, the risk of double counting is very low
- Costs of adverse events are included in the company's base case
  - → EAG prefers to include company's scenario including AE disutilities in base case
- However, notes that several AEs are not included in model at all e.g. musculoskeletal and connective tissue disorders, infections

Should adverse event disutilities be included in the model?

Abbreviations: AE, adverse events; EQ-5D, EuroQol 5-dimension

Response rates in the model

Summary of approaches to calculate probability of achieving 16-week composite outcome

Timepoint	OLYMPIA 1		OLYMPIA 2		Pooled OLYMPIA 1&2	
	Nemo, N = 190	Placebo, N = 96	Nemo, N = 183	Placebo, N = 91	Nemo, N = 373	Placebo, N = 187
16-week response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16-week unadjusted proportional difference		[redacted]		[redacted]		[redacted]
16-week strata adjusted proportional difference		[redacted]		[redacted]		[redacted]

EAG notes:

- Company's calculation assumes all missing data are non-responders
- EAG would prefer to include relative effect sizes for composite outcome rather than raw data

Composite PP NRS and IGA response data from OLYMPIA trials

Week	Nemolizumab	BSC	Source
Week 16	[redacted]	[redacted]	OLYMPIA 1
Week 16	[redacted]	[redacted]	OLYMPIA 2
Week 16	[redacted]	[redacted]	OLYMPIA 1 and 2
Week 24	[redacted]	[redacted]	OLYMPIA 1
Week 16/24	[redacted]	[redacted]	OLYMPIA 1 (Week 24) and OLYMPIA 2 (Week 16)

- Likely small impacts on ICER
- Important to consider the impact of integrating the available 24-week data into the model – company has provided scenarios

Abbreviations: PP NRS, peak pruritic numerical rating scale; IGA, investigators global assessment; ICER, incremental cost-effectiveness ratio; NR, not reported; BSC, best supportive care

Link back to Model overview

Response rates in TA955

Committee took into account company's and EAG's preferred definition of response

Comparison of composite response definitions used:

TA955 Company	TA955 EAG	Nemolizumab ID6451 (this appraisal)
• WI-NRS improvement ≥4 • IGA-PN-S reduction ≥1	• WI-NRS improvement ≥4 • IGA PN-S 0 or 1	• Nodule reduction ≥ 4 PP NRS • IGA score 0 or 1 + improvement ≥2 points

NB. Primary outcome in PRIME trials of dupilumab was WI-NRS improvement ≥4 alone (Worst Itch-Numerical Rating Scale)

Abbreviations: WI-NRS, Worst Itch Numerical Rating; IGA PN-S, Investigator's Global Assessment for Prurigo Nodularis Stage

Treatment discontinuation

Small ICER impact

EAG considers long-term discontinuation in both arms to be highly uncertain

Company

- For nemolizumab, discontinuation calculated from LTE study: probability of [redacted] applied in each cycle
- For BSC, discontinuation calculated from OLYMPIA 1

EAG comments

- Company states all patients in nemolizumab discontinuation calculation are from OLYMPIA 1 and 2 but unclear from numbers whether some came from phase 2 study
- Definition of response used to inform conditional treatment discontinuation calculation may not be aligned with composite response definition in model
- Stated methodology for calculating treatment discontinuation may not be aligned with the probability included in the model – EAG suggests an alternative approach to calculate probability of [redacted]
- Numerator in calculation is [redacted] so probability is highly uncertain as small changes in discontinuation events would have substantial relative impact
- Company's estimate of nemolizumab treatment discontinuation may be an underestimate
- Including placebo treatment discontinuation probability unlikely to be generalisable to best supportive care treatment adherence in UK clinical practice – EAG would prefer different approach to modelling BSC where a discontinuation assumption would not be required

→ EAG has presented scenario analyses exploring the impact of discontinuation rates

Abbreviations: LTE, long-term extension; BSC, best supportive care

Link back to Model overview

Treatment effect waning

EAG considers highly uncertain

Unknown ICER impact

Loss of response to treatment in company model, based on TA955

Treatment	Loss of response to treatment (%)			
	Year 2	Year 3	Year 4	Year 5 onwards
Nemolizumab	2.8%	8.6%	9.1%	9.1%
BSC	25.0%	50.0%	75.0%	100.0%

EAG comments

- May risk double counting treatment discontinuation because derived from different sources of evidence
- Mechanism of action of nemolizumab different to dupilumab – treatment effect waning could be lower for nemolizumab
- Treatment waning effects for BSC are based on the values used in TA534 for atopic dermatitis (from ARCADIA 1 study)
    - EAG does not consider these data to be generalisable to the PN population
    - Modelling approach is overly complicated

Abbreviations: BSC, best supportive care; PN, prurigo nodularis

Link back to Model overview

Utility values in TA955 dupilumab

Committee conclusions:

- Not enough evidence to support different utility values by treatment arm for non-responders at week 24 (start of Markov model)
    - Prefer to used pooled non-responder utility values
- After loss of response, utilities should return to baseline values after 6 months (when compared to the company's approach of utility waning gradually over 2 years)

Comparison of EQ-5D index scores from OLYMPIA 1& 2 versus TA955

Source	OLYMPIA 1 & 2 trials						PRIME & PRIME 2 trials (TA955)	
Time point	Response		Non-response		All (weighted average)			
	Nemo	BSC	Nemo	BSC	Nemo	BSC	Dupilumab	BSC
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.643	0.662
12 weeks	-	-	-	-	-	-	0.766	0.735
16 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
24 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.779	0.729

Abbreviations: BSC, best supportive care

Link back to Key issue: Utilities

BSC treatment basket

Company base case different to TA955

	Company base case		OLYMPIA 1+2			TA955 EAG clinical expert
Treatment	Response	Non-Response	Nemo	BSC	Pooled	
Antihistamines	5%	30%	20%	29%	21%	~50%
Emollients	100%	100%	19%	24%	13%	100%
TCS	20%	100%	15%	10%	1%	>50%
TCI	30%	100%	1%	0%	23%	~10%
Systemic corticosteroids	0%	15%	2%	2%	2%	30%-50%
Immunosuppressants	0%	77% (MTX)	1%	0%	1%	20%-50% (Ciclo, MTX)

Treatment	Responders	Non-responders	TA955
Antihistamines	70mg	70mg	Not included
Emollients	250g/ml per week	500ml per week	NR
TCS	7.5g	45g	50g
TCI	7.8g	30g	16.67g
Systemic corticosteroids	0mg	12.5mg	Not included
Immunosuppressants (MTX)	0mg	20mg (oral)	Not included

EAG comments

- Also substantial differences between TCS and TCI use
- EAG scenario analysis uses TA955 dose assumptions

Abbreviations: TCS, topical corticosteroids; TCI, topical calcineurin inhibitors; Ciclo, cicosporin; MTX, methotrexate

Link back to Clinical trial designs
Link back to Model overview

EAG preferred BSC per cycle cost

EAG prefers to include wastage and explores alternate approaches

	Company		EAG corrected company approach		EAG corrected company approach + wastage		TA955 TCS/TCI dosage assumptions + wastage		OLYMPIA shares + company dosage + wastage	
Treatment	R	NR	R	NR	R	NR	R	NR	R	NR
Antihistamines	£0.41	£2.48	£0.45	£2.70	£0.48	£2.89	£0.48	£2.89	£1.86	£1.86
Emollients	£131.32	£262.64	£167.06	£334.13	£173.02	£339.60	£173.02	£339.60	£22.37	£44.75
TCS	£7.02	£210.54	£7.02	£185.49	£7.53	£189.60	£42.66	£213.30	£0.25	£1.32
TCI	£66.84	£891.21	£57.18	£733.11	£59.01	£758.70	£126.45	£421.50	£43.57	£167.57
Systemic corticosteroids	£0.00	£0.52	£0.00	£5.51	£0.00	£5.91	£0.00	£5.91	£0.00	£0.66
Immunosuppressants (MTX)	£0.00	£19.06	£0.00	£18.83	£0.00	£18.94	£0.00	£18.94	£0.00	£0.22
Total	£205.60	£1,386.46	£231.71	£1,279.77	£240.04	£1,315.64	£342.61	£1,002.14	£68.06	£216.38

Abbreviations: MTX, methotrexate; NR, Non-Responder; R, Responder; TCI, topical calcineurin inhibitor; TCS. topical corticosteroid

Further EAG deterministic scenario analyses

EAG scenarios applied to company base case

No.	Deterministic scenario (applied to company base case)	ICER (£/QALY) versus BSC
1	**Company base case (corrected)**	**£34,657**
12	Strata adjusted effect size from: A) OLYMPIA 1 alone	£35,006
13	Strata adjusted effect size from: B) OLYMPIA 2 alone	£34,632
14	Strata adjusted effect size from: all 3 nemolizumab studies	£34,591
15	Equalise the treatment basket for responders and non-responders: OLYMPIA 1 & 2 treatment basket	£35,361
16	Equalise the treatment basket for responders and non-responders: TA955 EAG clinical expert treatment basket	£36,314
17	TCI dose 16.67g for all + TCS dose of 50g for all	£35,578
18	Nemolizumab discontinuation = [redacted], Total who discontinued from the LTE study)	£35,443
19	Nemolizumab discontinuation = [redacted], Total randomised for OLYMPIA with a response that discontinued from LTE)	£34,721
20	Remove BSC discontinuation	£34,781

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; TCI topical calcineurin inhibitors; TCS, topical corticosteroids; LTE, long-term extension

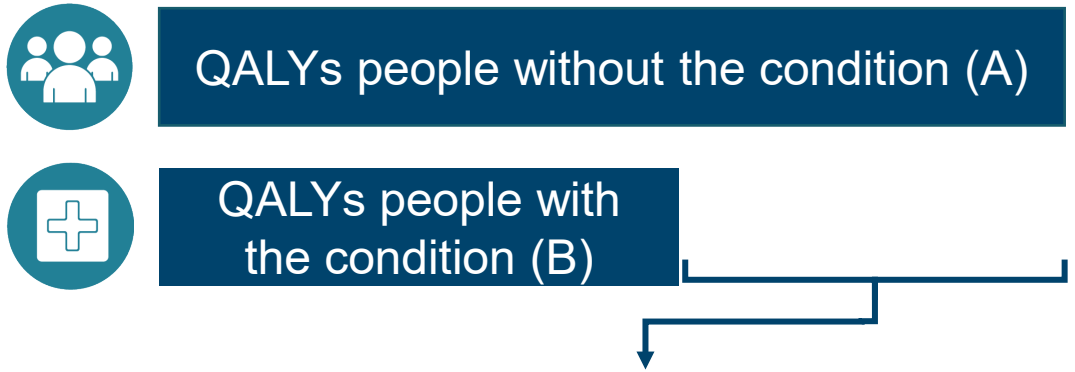
Link back to EAG scenario analyses – utility values

QALY weightings for severity

No severity modifier applies in this appraisal
- Weighting not calculated by company
- EAG agrees not relevant

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Severity modifier calculations and components:



Health lost by people with the condition:
- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

Abbreviations: QALY, quality-adjusted life year