Dupilumab for treating moderate to severe prurigo nodularis

For public – fully redacted

Technology appraisal committee B 02nd August 2023

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Key issues for discussion

Table 1 Key issues

Issue	ICER impact
Exclusion of antihistamines, oral steroids, immunosuppressive therapies and antidepressants as comparators	Unknown (likely increase) 
BSC in PRIME does not adequately reflect interventions used in NHS clinical practice	Unknown (likely increase) 
Limited applicability of the PRIME trial populations to the NHS population	Unknown (likely increase) 
Treatment effect by patient weight	Unknown (likely increase) 
Response criteria in the model	Small 
Long-term treatment effect and response waning	Small 
Utility values for non-responders	Large 

Abbreviations: BSC, best supportive care

Dupilumab (Dupixent, Sanofi)

Table 2 Technology details

Marketing authorisation	Dupilumab is indicated for treatment of moderate-to-severe prurigo nodularis UK marketing authorisation granted by Medicines and Healthcare products Regulatory Agency (MHRA) in April 2023
Mechanism of action	Dupilumab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signaling
Administration	Self-administered by subcutaneous injection into the thigh or abdomen, except for 2 inches (5 cm) around the navel, using a single-use pre-filled syringe or pen Initial dose of 600 mg (two 300 mg injections administered in different injection sites), followed by 300 mg given every other week
Price	• List price per pre-filled pen/syringe = £1,264.89 per 2mL (150mg/mL) • List price for first 12 months of treatment = £16,500 for 27 x 2mL pre-filled pen/syringe • Simple discount patient access scheme (PAS)

Abbreviations: IL, interleukin; IG, immunoglobin

Background on prurigo nodularis

Causes

- Cause of prurigo nodularis is unknown
- Associated with abnormal levels of nerve fibres, neuropeptides, and cytokine producing immune cells

Epidemiology

- Estimated 0.03% of people in England have prurigo nodularis
- A study conducted by Sanofi of patient records in England between 2007 and 2019 found a mean age of 61 in prurigo nodularis with 43% of cases reported in males

Symptoms and prognosis

- Prurigo nodularis is characterised by skin nodules that have a rough, thick surface.
- They are usually darker than the skin around them, and may show scabbing, crusting, or scratches
- Itchiness (pruritis) precedes the development of nodules. The nodules are uncomfortable and can cause distress
- Prognosis depends on the ability to stop the cycle of itching and scratching

Diagnosis and grading

- Itching and characteristic nodules are usually enough for diagnosis, but skin biopsy may also be taken
- Grading of prurigo nodularis usually uses the Investigator's Global Assessment for Prurigo Nodularis (IGA-PN) which classifies severity on a 5-point scale (0-4); above Grade 3 is moderate, Grade 4 is severe
- DLQI is also important for considering impact of disease and response

Abbreviations: DLQI, Dermatology Life Quality Index

Scales used in prurigo nodularis

Worst Itch Numerical Rating Scale (WI-NRS)

- WI-NRS is a scale used to assess the severity of itching
- It is a single-item patient-reported outcome measure in which patients indicate the intensity of the worst itching they experienced over the past 24 hours
- The scale ranges from 0 (labelled as “no itching”) to 10 (labelled as “worst itching imaginable”)
- The WI-NRS has been validated in assessing many conditions, including prurigo nodularis (Kimel et al. 2020)

Investigator’s Global Assessment for Prurigo Nodularis (IGA-PN)

- IGA-PN is a scale used to assess the severity of prurigo nodularis
- The possible scores are:
    - **Grade 0 (clear):** no nodules (zero nodules)
    - **Grade 1 (almost clear):** rare, flattened lesions, with no more than five dome-shaped palpable nodules (approximately 1 to 5 nodules)
    - **Grade 2 (mild):** few, mostly flattened lesions, with small number of dome-shaped palpable nodules (approximately 6 to 19 nodules)
    - **Grade 3 (moderate):** many lesions, partially flattened and dome-shaped palpable nodules (approximately 20 to 100 nodules)
    - **Grade 4 (severe):** abundant lesions, majority are dome-shaped palpable nodules (>100 nodules)

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

Clinical perspectives

Submission from the British Association of Dermatology

- There are very limited options for effective treatment of patients with severe or treatment resistant prurigo nodularis
- Dupilumab would make a great difference to patients who have severe or treatment resistant disease
- People with prurigo nodularis and concomitant eczema would experience particular benefit
- Dupilumab is likely to be used in patients in whom topical anti-inflammatory/phototherapy/systemic anti-inflammatory medications have been ineffective or contra-indicated
- The evidence that dupilumab reduces pruritus, improves QoL and reduces severity of prurigo nodularis is more robust than existing treatments

Most dermatology departments will have used this technology for other disease indications

Sustained reduction in itch severity (WI-NRS), and consequently improvement in QoL and quality of sleep, is one of the most important outcomes

Abbreviations: QoL, quality of life; WI-NRS, worst itch numerical rating scale

Patient perspectives

Submission from Prurigo Nodularis International

- Prurigo Nodularis is a devastating, life changing disease. It has a deeply detrimental impact on all aspects of patient's lives
- Achieving a diagnosis is extremely challenging due to a general lack of awareness of the condition among the medical community.
- There are no established treatment or care pathways currently in place nation-wide for this group of patients, often depending on local provision
- Patients must often go from trying one treatment to the next, enduring often potentially dangerous and potent side effects for little to no benefit, and even when an empirical treatment helps, it's not clear why and may not necessarily help another patient.
- The disease if not contained it spreads often to cover a significant part of the body. Patients are also at risk of developing other conditions alongside PN as a result of the long-standing inflammation.

There is little physical, mental and emotional peace as the itch is constant. It is distressing. Patients can experience a combination of itching, pain, burning and stinging sensation.

The lack of dedicated treatment options means that the disease is left unchecked with the potential to destroy patient's lives

Abbreviations: PN, prurigo nodularis

Treatment pathway for prurigo nodularis

Treatments generally follow a 'stepped approach'

- No established pathway for prurigo nodularis; 'a stepped approach' is generally used in current clinical practice
- Treatment can be stepped up or down according to the severity of the condition

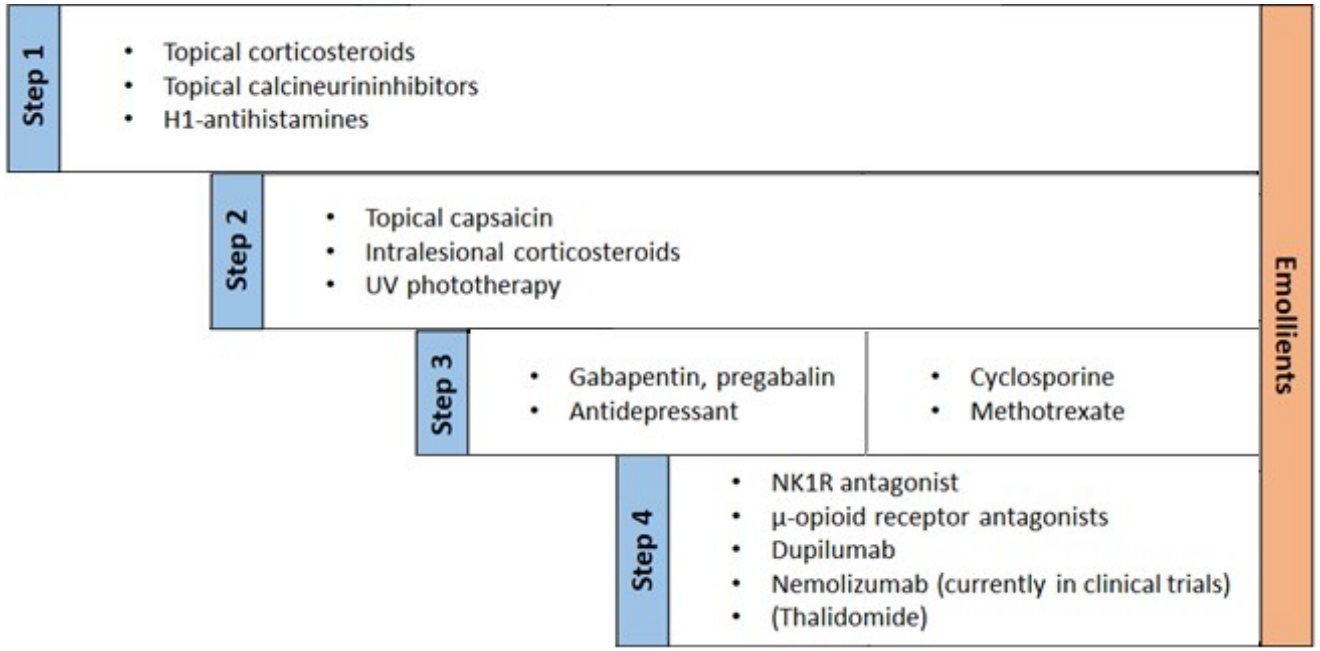


Figure 1 'Stepped approach' treatment pathway

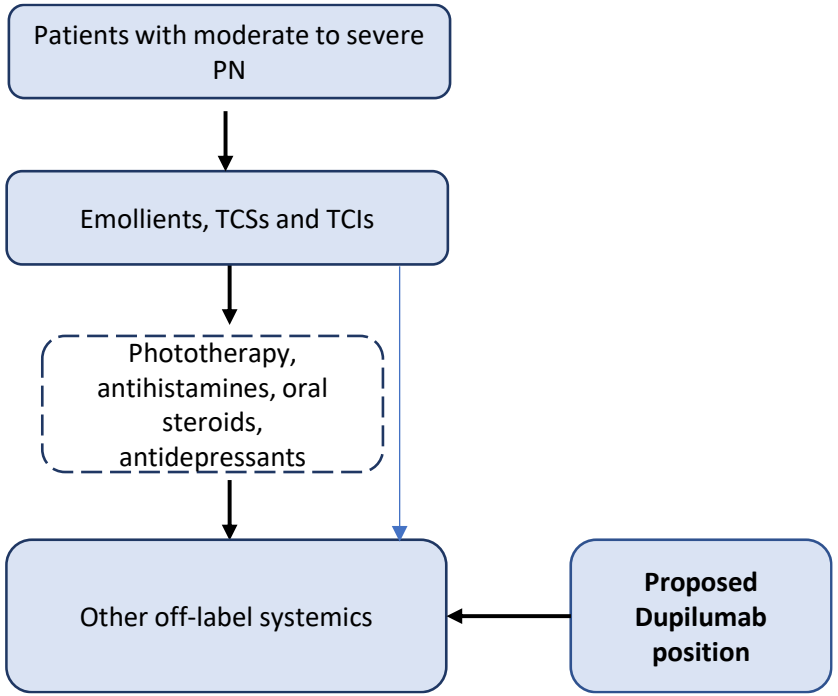


Figure 2 Expected position of dupilumab

Are the treatments used in step 4 of the treatment pathway used in NHS practice?

Abbreviations: PN, prurigo nodularis; TCI, Topical calcineurin inhibitors; TCS, topical corticosteroids

Decision problem

Table 3 Decision problem

	Final scope	Company	EAG comments
Population	Adults with moderate to severe PN that had inadequate response or intolerance to existing topical treatments.	No change from scope	Company decision problem broadly in line with NICE scope but differences in characteristics between trial and NHS populations. Only 3 people from UK in trials but not enough data to determine what impact this has on results.
Intervention	Dupilumab in combination with topical emollients, TCSs and TCIs.	No change from scope	No EAG comments
Comparators	Established clinical management without dupilumab, including topical emollients, TCSs, TCIs, antihistamines, oral steroids, phototherapy, immunosuppressive therapies, SSRIs and SNRIs.	Only includes topical emollients, TCSs, and TCIs	Company's justification for excluding phototherapy as a comparator appears appropriate, as phototherapy is a short-term treatment and is associated with availability and logistical issues. However, the exclusion of antihistamines, oral steroids, immunosuppressive therapies, and antidepressants does not align with the best supportive care used in the NHS.

Abbreviations: EAG, external assessment group; PN, prurigo nodularis; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCI, Topical calcineurin inhibitors; TCS, topical corticosteroids

Decision problem

Table 3 ctd. Decision problem

	Final scope	Company	EAG comments
Outcomes	• Measures of disease severity • Measures of symptom control including improvement in itch • Disease-free period/ maintenance of remission • Time to relapse • Adverse effects • HRQoL.	Excludes disease-free period/ maintenance of remission and time to relapse	EAG does not agree with excluding disease-free period/maintenance of remission and time to relapse/prevention of relapse outcomes, as these are important outcomes to patients. The company stated that the trials were insufficiently powered for these outcomes. EAG also notes lack of longer-term data does not allow for meaningful analysis of these outcomes

Abbreviations: EAG, external assessment group; HRQoL, health-related quality of life

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials

Company provided a systematic literature review for clinical effectiveness at technical engagement. It considers PRIME and PRIME-2 are key trials

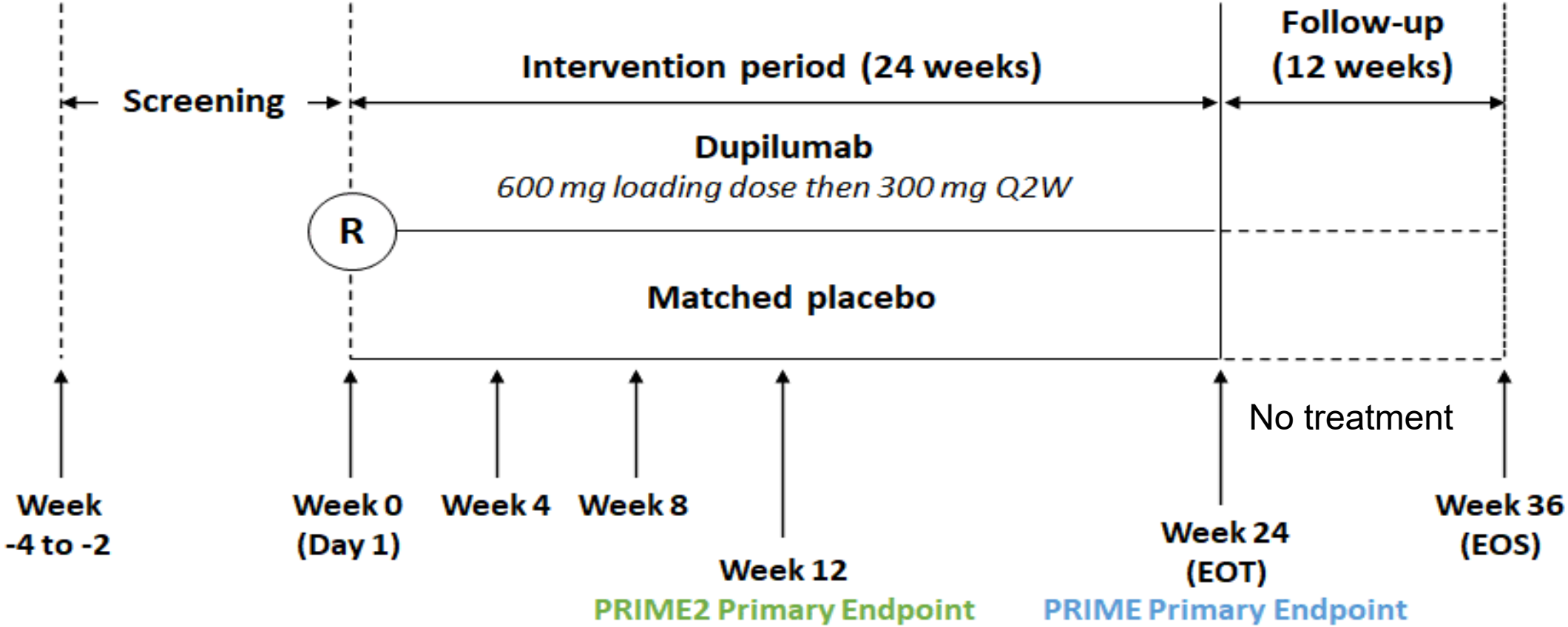
Table 4 Clinical trial designs and outcomes

	NCT04202679 (PRIME2)	NCT04183335 (PRIME)
Design	Phase 3 randomised, double-blind, placebo-controlled study	
Population	Adults with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable	
Intervention and comparator	**Intervention**: Dupilumab + BSC **Comparator**: Placebo + BSC	
Duration	24 weeks (+untreated follow-up period of 12 weeks)	
Primary outcome	Proportion achieving WI-NRS improvement (reduction) of ≥4 points from baseline	
Locations	57 centres in Canada, Chile, France, Hungary, Italy, Portugal, Republic of Korea, Spain, Taiwan, UK and US	63 centres in US, Argentina, Mexico, Mainland China, Japan, Russian Federation, Republic of Korea and France
Used in model?	Yes	Yes

Abbreviations: BSC, best supportive care; PN, prurigo nodularis; WI-NRS, Worst Itch Numerical Rating Scale

PRIME and PRIME2 study design

Figure 3 Study design of PRIME trials



Data available at week 12, week 24, and week 36

Were low or medium strength TCIs/TCSs allowed after week 24?

Abbreviations: EOS, end of study; EOT, end of treatment; Q2W, every 2 weeks; R, randomisation

PRIME and PRIME2 primary analysis

In PRIME and PRIME2 the mean percentage with at least a 4-point improvement from baseline in WI-NRS was higher for dupilumab compared with placebo.

Table 5 Prime trials primary analysis

Endpoint	PRIME2		PRIME		Pooled ITT analysis	
	BSC (n=82)	Dupilumab (n=78)	BSC (n=76)	Dupilumab (n=75)	BSC (n=158)	Dupilumab (n=153)
Patients with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 12						
Responders, n (%)	18 (22.0)	29 (37.2)	12 (15.8)	33 (44.0)	30 (19.0)	62 (40.5)
Nominal p value vs. BSC[a]	0.0216		0.0003		<0.0001	
OR, 95% CI vs. BSC[b]	2.3 (1.08, 5.00)		4.3 (1.86, 9.77)		3.1 (1.77, 5.43)	
RRD (%), 95% CI vs. BSC[b]	16.8 (2.34, 31.16)		29.2 (14.49, 43.81)		22.7 (12.40, 33.08)	
Patients with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 24						
Responders, n (%)	16 (19.5)	45 (57.7)	14 (18.4)	45 (60.0)	30 (19.0)	90 (58.8)
Nominal p value vs. BSC[a]	<0.0001		<0.0001		<0.0001	
OR, 95% CI vs. BSC[b]	9.0 (3.56, 22.66)		6.5 (2.78, 15.41)		7.6 (4.03, 14.24)	
RRD (%), 95% CI vs. BSC[b]	42.6 (29.06, 56.08)		42.7 (27.76, 57.72)		42.7 (32.60, 52.71)	

Abbreviations: BSC, best supportive care; CI, confidence interval; ITT, intention to treat; OR, odds ratio; RRD, response ratio difference; WI-NRS, Worst Itch Numerical Rating Scale

Adverse events

Table 6 Adverse events reported in PRIME trials

Adverse event	BSC (N=157)	Dupilumab (N=152)
Any TEAE, n (%)	89 (56.7)	97 (63.8)
Severe TEAE, n (%)	9 (5.7)	5 (3.3)
Treatment emergent SAE, n (%)	12 (7.6)	7 (4.6)
TEAE leading to death, n (%)	0	0
TEAE leading to permanent treatment continuation, n (%)	4 (2.5)	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AESI, adverse event of special interest; BSC, best supportive care; IMP, investigation medicinal product; SAE, serious adverse event; TEAE, treatment emergent adverse event

Key issue: Exclusion of comparators

Background

- The final scope included topical emollients, TCSs, TCIs, antihistamines, oral steroids, phototherapy, immunosuppressive therapies, SSRIs and SNRIs as comparators as part of BSC
- The company included only topical emollients, TCSs, TCIs in its decision problem

Company

- There is a lack of RCT evidence to support the efficacy of antihistamines, oral steroids, phototherapy, immunosuppressive therapies and antidepressants in treatment of prurigo nodularis.
- Phototherapy is used earlier in the treatment pathway and so cannot be regarded as a direct comparator

EAG comments

- In NHS practice, BSC is likely to include one or more of: a high- or super-potent topical corticosteroid, a systemic immunosuppressant, an antidepressant, antihistamines, and oral steroids
- Many of the excluded comparators were not permitted in PRIME trials, meaning people received a much lower level of BSC than people in NHS practice
- Agrees with the exclusion of phototherapy but does not agree with exclusion of other comparators

Are the comparators included in the company's decision problem appropriate?

Abbreviations: BSC, best supportive care; PN, prurigo nodularis; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; RCT, randomised controlled trial; TCI, Topical calcineurin inhibitors; TCS, topical corticosteroids

Key issue: Generalisability of BSC in PRIME trials to NHS practice

Background

- Both PRIME trials prohibited the use of various treatments used for prurigo nodularis including, antihistamines, oral steroids, phototherapy, immunosuppressive therapies, SSRIs and SNRIs
- High- and super-potent topical corticosteroids restricted to rescue medication, occlusion was prohibited

Company

- Clinical experts say there is no structured treatment pathway for managing PN beyond topical therapy
- Evidence for the use of therapies after topical treatment is weak, often only used as adjunct therapy
- Experts highlighted that PN treatments have an unpredictable clinical response, may not be tolerated due to age or comorbidities
- Considers BSC treatments in the trials to be acceptable for decision making purposes

EAG comments

- For PRIME trial results to be considered applicable to the NHS setting, it is important that BSC used in the PRIME trials broadly reflects the interventions currently used in the NHS
- EAG's advisers indicated that in the NHS, systemic therapies, particularly immunosuppressive therapies (such as methotrexate), would form a key aspect of BSC
- EAG's advisors estimated use of several BSC therapies in the moderate-to-severe PN NHS population

Abbreviations: BSC, best supportive care; EAG, external assessment group; PN, prurigo nodularis; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors

Key issue: Generalisability of BSC in PRIME trials to NHS practice

Table 7 BSC used before and during the PRIME trials compared to estimated usage in the NHS

BSC component	Use in PRIME trials pooled cohort (% of cohort)			Estimated use* in moderate-to-severe PN NHS patients (%)
	Before entry	At baseline	During trial	
Low-medium potency TCS	Unclear, though 98% had used TCS	Unclear: 59% TCS[a] or TCI	NR	>50%
High or super potent TCS		0 (prohibited)	[redacted]	>80%
Occlusion of TCS	[redacted]	[redacted]	[redacted]	~30%
TCIs	[redacted]	Unclear: 59% TCS or TCI	[redacted]	~10%
Antihistamines	[redacted]	0 (prohibited)	[redacted]	~50%
Systemic CS	[redacted]	0 (prohibited)	[redacted]	30%-50%
Methotrexate	[redacted]	0 (prohibited)	[redacted]	~50%
Cyclosporine	[redacted]	0 (prohibited)	[redacted]	~20%
Antidepressants	[redacted]	[redacted] (prohibited[b])	[redacted]	~10%

Do the treatments used in the trial adequately represent NHS practice?

Abbreviations: BSC, best supportive care; CS, corticosteroids; NR, not recorded; PN, prurigo nodularis; TCI, Topical calcineurin inhibitors; TCS, topical corticosteroids

Key issue: Generalisability of trial population to NHS population

Background

- Mean age of pooled PRIME trial cohort was under 50 and the mean weight was around 74kg
- [redacted] of the PRIME cohort had previously used methotrexate

Company

- Pooled sub-group analysis of people with and without prior exposure to immunosuppressants in the trials [redacted]
- Case notes review revealed that [redacted] of PN patients had treatment with immunosuppressants in England
- Experts indicate patient responses to topical steroid and systemic agents were usually disappointing
- There is no or very weak evidence for use of any unlicenced systemics for the treatment of PN

EAG comments

- Methotrexate is a key treatment used in the NHS population
- EAG's advisors would expect higher mean age and weight, [redacted]
- Methotrexate-naive trial population may be more likely to achieve response criteria

Is age in the trial similar enough to NHS practice to allow for decision making?

Abbreviations: EAG, external assessment group; PN, prurigo nodularis

Key issue: Treatment effect by patient weight

Background

- Pre-specified subgroup analyses were conducted using WI-NRS improvement of ≥4 points from baseline
- [redacted]
- [redacted]

Company

- [redacted]
- [redacted]
- Results from treatment with dupilumab in atopic dermatitis indicated that a weight of ≥100 kg did not significantly affect efficacy

EAG comments

- [redacted]
- [redacted]
- [redacted]

Abbreviations: EAG, external assessment group; WI-NRS, Worst Itch Numerical Rating Scale

Key issue: Treatment effect by patient weight

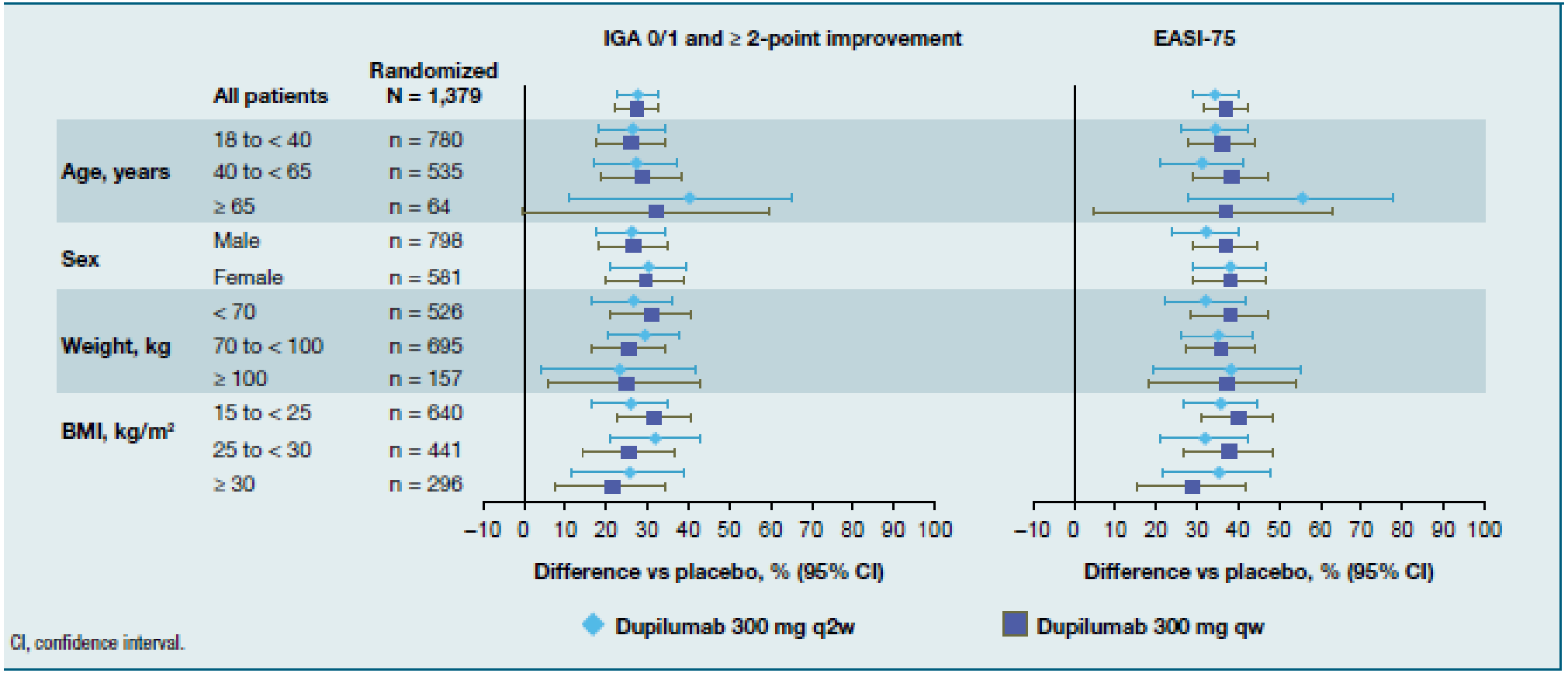


Figure 4 Sub-group analysis of EASI and IGA from SOLO-1 and 2 (dupilumab for treating atopic dermatitis) based upon prespecified baseline demographics, including age, sex, weight and body mass index (BMI)

Does patient weight significantly affect the treatment effect of dupilumab?

Abbreviations: CI, confidence interval; EASI, Eczema Area and Severity Index; IGA, Investigators Global Assessment; q2w, every 2 weeks; qw, once weekly

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

Figure 5 Model structure

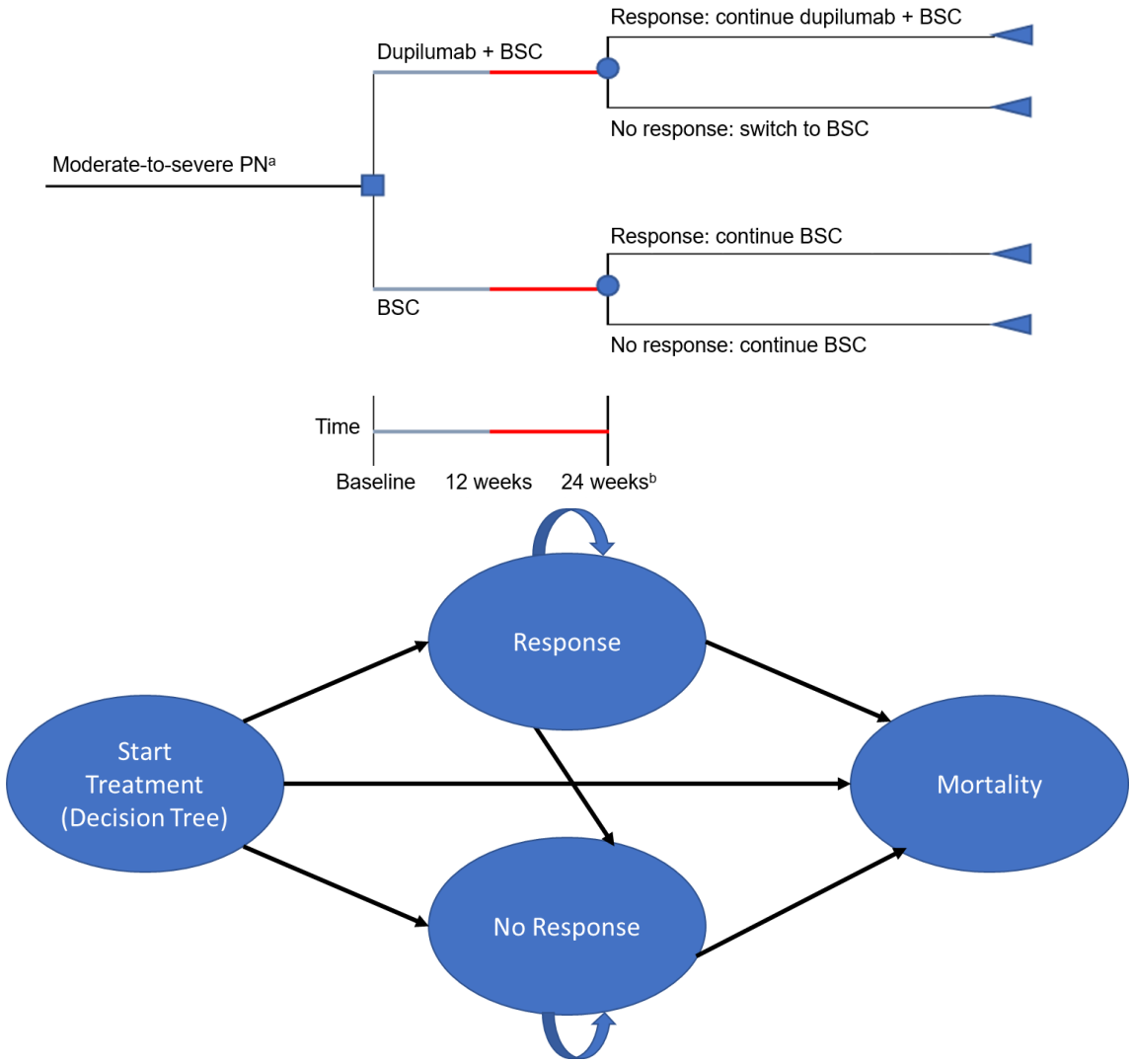


Table 8 Model overview

Model structure	Cohort model with decision tree and Markov model
Perspective	UK NHS and PSS
Time horizon	42 years (mean age at baseline 49.5 years)
Cycle length	Decision tree = 24 weeks Markov model = 12 weeks
Discounting	3.5% per annum for costs and benefits

EAG consider model structure broadly representative of the natural course of PN

Abbreviations: BSC, best supportive care; EAG, external assessment group; PN, prurigo nodularis

Key issue: Response criteria in the model

Background

- Criteria used in the model to define response at week 24 was a composite of WI-NRS improvement ≥4 and IGA-PN-S reduction ≥1

Company

- Experts suggested that IGA PN-S reduction ≥ 1 captures meaningful response at week 24, extremely challenging to reach IGA-PN-S score of 0 or 1 within 24 weeks
- Pooled mean baseline IGA-PN-S score from the trials was [redacted], reducing IGA-PN-S by ≥ 1 in these patients would be regarded as a substantial and meaningful improvement by clinicians and patients

EAG comments

- It is reasonable to use a composite response criteria. IGA-PN-S measures the number of nodules and WI-NRS measures the level of itchiness
- Limited justification for using IGA-PN-S reduction ≥1 as part of a composite response criteria which is not a key primary or secondary outcome measure in trials
- A key secondary endpoint in the trials was the proportion with IGA PN-S 0 or 1 score at week 24
- More appropriate to use IGA PN-S 0 or 1 combined with WI-NRS improvement ≥4 score in the model
  - Greater consistency with trials and more indicative of significant impact on symptom control

What is the most suitable response criteria?

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

Key issue: Long-term treatment effect and loss of response

Background

- Model includes all-cause annual treatment discontinuation rate in the dupilumab arm of [redacted], and annual loss of response probability of [redacted] applied in the BSC arm.
- Transition probabilities were based on these plus the probability of sustained response per year from the 'Response' to 'No response' treatment state in the model

Probability of sustained response	Year 2	Year 3	Year 4	Year 5+
Dupilumab +BSC (based on OLE study)	91.4%	97.2%	90.9%	90.9%
Probability of sustained response	**Year 2**	**Year 3**	**Year 4**	**Year 5+**
BSC (based on AD from TA534)	75%	50%	25%	0%

Company

- High BSC response is likely due to trial procedures and are unlikely to be maintained long term
- Loss of response post-trial is unlikely to be the same for dupilumab arm

EAG comments

- Very high annual loss of response rate for BSC combined with a low probability of sustaining response over time means that the predicted response rate for BSC at week 24 is short lived and diminishes very rapidly over time compared to dupilumab plus BSC

NICE

Abbreviations: AD, atopic dermatitis; BSC, best supportive care

Key issue: Long-term treatment effect and loss of response

Table 9 Week 36 response rates for responders to treatment at week 24 from the pooled ITT population of the PRIME2 and PRIME trials

	Week 24 responder		Week 24 Non-responder	
Response criteria	Dupilumab plus BSC, n(%)	BSC, n(%)	Dupilumab plus BSC, n(%)	BSC, n(%)
WI-NRS improvement ≥4 from baseline to week 36 for responders at week 24†				
Responder	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
IGA PN-S score 0 or 1 from baseline to week 36 for responders at week 24†				
Responder	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
WI-NRS improvement ≥4 and IGA-PN-S score of 0 or 1 from baseline to week 36 for responders at week 24†				
Responder	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]

What is the most suitable implementation of loss of response and probability of sustained response? Are these results representative of loss of response to BSC in the UK?

Abbreviations: BSC, best supportive care, IGA-PN-S, Investigator Global Assessment For Prurigo Nodularis Stage; MI, multiple imputation; WI-NRS: Worst itch Numerical Rating Scale.

Key issue: Utility values for non-responders

Company

- Utility values in the model were derived from the PRIME trials at 3 timepoints (baseline, week 12, and week 24) using EQ-5D-5L responses mapped to the EQ-5D-3L
- QoL evidence for dupilumab in PN was generated by the trials, which are the best available evidence
- Level of response required is high, so similar utility values are expected for responders
- There are more likely to be partial responders in the dupilumab group than the BSC group because the inhibition of IL4/13 targets the underlying cause of disease, so group utility will be higher

	Time in the model	Dupilumab plus BSC	BSC
Decision tree model	Baseline (pooled arms)	[redacted]	[redacted]
	Week 12-24 (regardless of response)	[redacted]	[redacted]
	At week 24 (baseline in Markov model):	[redacted]	[redacted]
Markov model	Time since becoming a non-responder	Dupilumab plus BSC non-responders	BSC non-responders
	0 – 6 months	[redacted]	[redacted]
	6 – 12 months	[redacted]	[redacted]
	1 – 2 years	[redacted]	[redacted]
	2+ years	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; IL, interleukin; PN, prurigo nodularis

Key issue: Utility values for non-responders

EAG comments

- All non-responders receive BSC only so separate utility values by treatment arm isn't appropriate
- There is a much larger difference in utility weights between treatment arms in non-responders ([redacted]) than in responders ([redacted]) at week 24.
- Considers that pooled (across treatment arms) week 24 utility values for non-responders from the trials would be more appropriate for all non-responders
- Considers that utility after loss of response should last for 6 months

	Time in the model	Dupilumab plus BSC	BSC
Decision tree model	Baseline (pooled arms)	[redacted]	[redacted]
	Week 12-24 (regardless of response)	[redacted]	[redacted]
	At week 24 (baseline in Markov model):	[redacted]	[redacted]
Markov model	Time since becoming a non-responder	Dupilumab plus BSC non-responders	BSC non-responders
	0 – 6 months	[redacted]	[redacted]
	6+ months	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; IL, interleukin; PN, prurigo nodularis

Key issue: Utility values for non-responders

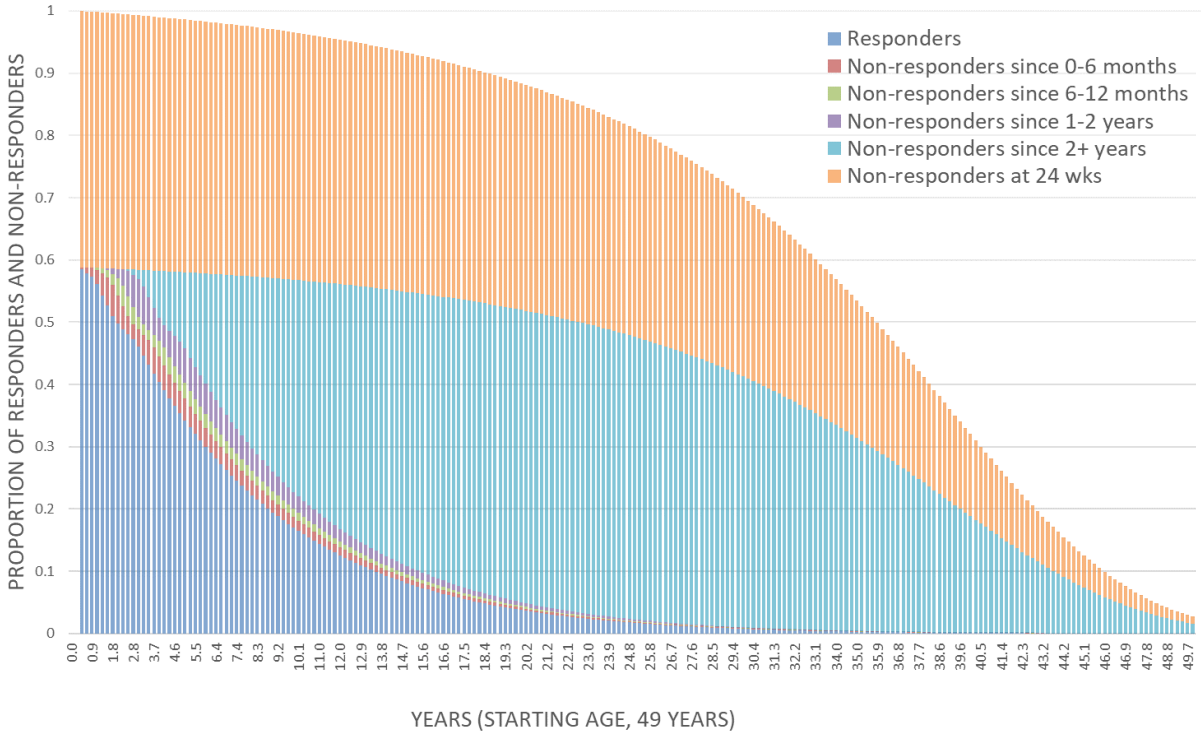


Figure 6 Markov trace of dupilumab arm

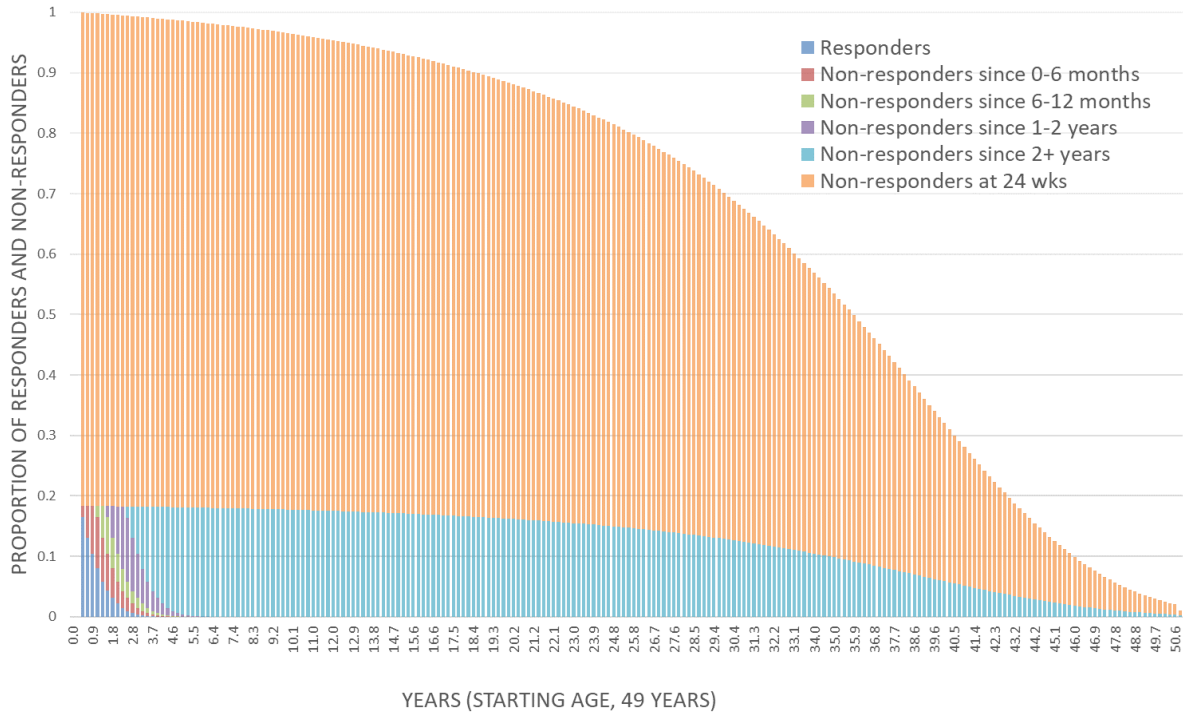


Figure 7 Markov trace of BSC arm

What are the most suitable utility values for non-responders?

Abbreviations: BSC, best supportive care

Company and EAG preferred base case assumptions

Table 12 Company and EAG preferred base case assumptions

Base case preferred assumptions	Company	EAG
Response criteria	WI-NRS improvement ≥4 and IGA-PN-S reduction of ≥1	WI-NRS improvement ≥4 and IGA-PN-S score of 0 or 1
BSC loss of response	Annual probability of loss of response ([redacted]) as well as loss of sustained response	Annual probability of loss of response for BSC set to 0% (includes loss of sustained response)
Non-responder utility values	Separate utility values for dupilumab arm ([redacted]) and BSC arm ([redacted]) non-responders	Same utility value by treatment arm for non-responders based on week 24 pooled value for non-responders ([redacted])
Non-responder utility rebound after treatment discontinuation	Utility values for non-responders decrease over 2 years at a rate based on the results of a structured expert elicitation.	Utility values for non-responders assumed to hold only for 6 months after discontinuation then rebound to baseline utility ([redacted])

Abbreviations: BSC, best supportive care; EAG, external assessment group; IGA PN-S, Investigator's Global Assessment for Prurigo Nodularis Stage; WI-NRS, Worst Itch Numerical Rating Scale

Cost-effectiveness results

Company base case results

Table 13 Company's deterministic results

Technologies	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£27,010

Table 14 Company's probabilistic results

Technologies	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	-	-	-
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,974

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life years

EAG's preferred assumptions and base case

Table 15 EAG preferred assumptions and base case

Scenario	Name	Inc. Costs (£)	Inc. QALYs	ICER, (£/QALY)
	Company's base-case	[redacted]	[redacted]	£27,010
1	Response criteria: WI-NRS improvement ≥4 and IGA-PN-S score of 0 or 1 from baseline to week 24	[redacted]	[redacted]	£25,279
2	All-cause discontinuation rate for BSC set to 0% (includes loss of sustained response on BSC)	[redacted]	[redacted]	£29,026
7	Same utility value by treatment arm for non-responders based on week 24 pooled value for non-responders	[redacted]	[redacted]	£29,176
12	Utility values for non-responders are assumed to hold constant only for first 6 mo. after treatment discontinuation, then rebound to baseline utility. Different utilities used for non-responders to treatment by week 24 and those who previously responded to treatment by week 24 but subsequently discontinued treatment and became a non-responders in the model	[redacted]	[redacted]	£32,763
1+2+7+12	**EAG base case**	[redacted]	[redacted]	**£37,291**

Abbreviations: BSC, best supportive care; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; IGA-PN-S, Investigator's Global Assessment for Prurigo Nodularis Stage; QALY, quality-adjusted life year; WI-NRS, Worst Itch Numerical Rating Scale

EAG's preferred assumptions and base case (cumulative)

Table 16 EAG preferred assumptions and base case with cumulative ICERs

Scenario	Name	Inc. Costs (£)	Inc. QALYs	ICER, (£/QALY)
	Company's base-case	[redacted]	[redacted]	£27,010
1	Response criteria: WI-NRS improvement ≥4 and IGA-PN-S score of 0 or 1 from baseline to week 24	[redacted]	[redacted]	£25,279
1+2	All-cause discontinuation rate for BSC set to 0% (includes loss of sustained on BSC)	[redacted]	[redacted]	£26,627
1+2+7	Same utility value by treatment arm for non-responders based on week 24 pooled value for non-responders	[redacted]	[redacted]	£29,995
1+2+7+12 EAG base case	Utility values for non-responders are assumed to hold constant only for the first six months after treatment discontinuation and then rebound to baseline utility. Different utilities used for non-responders to treatment by week 24 and those who previously responded to treatment by week 24 but subsequently discontinued treatment and became a non-responders in the model	[redacted]	[redacted]	£37,291
2+7+12	With response criterion: WI-NRS improvement ≥4 and IGA-PN-S reduction ≥ 1 from baseline to week 24 (response criteria in company base case)	[redacted]	[redacted]	£35,592

Abbreviations: BSC, best supportive care; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; IGA-PN-S, Investigator's Global Assessment for Prurigo Nodularis Stage; QALY, quality-adjusted life year; WI-NRS, Worst Itch Numerical Rating Scale

Company scenario results

Table 17 Company scenario results

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Response criteria: WI-NRS improvement ≥4	[redacted]	[redacted]	£28,210
No response waning applied	[redacted]	[redacted]	£26,851
Response waning AD Dermatologist survey + SEE	[redacted]	[redacted]	£28,082
Response waning AD Dermatologist survey + NICE estimates	[redacted]	[redacted]	£28,262
Response waning AD OLE study + SEE	[redacted]	[redacted]	£26,544
Inclusion of societal perspective	[redacted]	[redacted]	£12,158
Healthcare resource use– AD micro-costing	[redacted]	[redacted]	£26,661
Healthcare resource use –2019/2020 cost data	[redacted]	[redacted]	£27,652
Healthcare resource use-TA814	[redacted]	[redacted]	£27,389
Healthcare resource use-TA534	[redacted]	[redacted]	£23,255
Utility algorithm: Van Hout	[redacted]	[redacted]	£24,148
AD discontinuation rate	[redacted]	[redacted]	£26,218

Abbreviations: AD: atopic dermatitis; ICER: incremental cost-effectiveness ratio; NICE: National Institute for Health and Care Excellence; OLE: open-label extension; PN: prurigo nodularis; QALYs: quality-adjusted life years; SEE: structured expert elicitation; WI-NRS: Worst Itch Numerical Rating Scale..

Additional company scenarios in response to EAR

Table 18 Additional company scenarios

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
WI-NRS improvement ≥ 4 with IGA-PN-S score of 0 or 1, arm specific utility, no loss of sustained response applied on BSC, utility waning applied based on adjusted EAG numbers from the SEE, annualised loss of response on BSC arm [redacted]	[redacted]	[redacted]	£29,502
WI-NRS improvement ≥ 4 with IGA-PN-S reduction ≥ 1, arm specific utility, no loss of sustained response applied on BSC, utility waning applied based on adjusted EAG numbers from the SEE, annualised loss of response on BSC arm [redacted]	[redacted]	[redacted]	£31,100
WI-NRS improvement ≥4 and IGA-PN-S score of 0 or 1, arm specific utility, no loss of sustained response applied and waning used from TA534 to adjust utilities, annualised loss of response on BSC arm [redacted]	[redacted]	[redacted]	£30,285
WI-NRS improvement ≥ 4 with IGA-PN-S reduction ≥ 1, arm specific utility, no loss of sustained response applied and waning used from TA534 to adjust utilities, annualised loss of response on BSC arm [redacted]	[redacted]	[redacted]	£31,829

Abbreviations: BSC, best supportive care; EAG, external assessment group; ICER: incremental cost-effectiveness ratio; IGA-PN-S: Investigators Global Assessment for Prurigo Nodularis Stage; QALYs: quality-adjusted life years; SEE: structured expert elicitation; WI-NRS: Worst Itch Numerical Rating Scale.

EAG other scenario results

Table 19 Additional EAG scenarios

Scen. #	Name	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
3	Loss of sustained response removed, discontinuation rate maintained	[redacted]	[redacted]	£28,822
4	Alternative estimates for maintenance of treatment effect for dupilumab plus BSC	[redacted]	[redacted]	£24,629
5	Response to BSC at week 24 held constant over time	[redacted]	[redacted]	£106,039
6	25% of the response rate for BSC at week 24 held constant over time	[redacted]	[redacted]	£27,816
8	Same utility value by treatment arm for non-responders based on week 24 value for BSC non-responders	[redacted]	[redacted]	£29,919
9	Utility waning rates for dupilumab plus BSC non-responders set equal to BSC non-responders	[redacted]	[redacted]	£32,714
10	Separate utility waning rates by treatment arm for non-responders based on the results of the SEE	[redacted]	[redacted]	£32,343
11	Separate utility waning rates by treatment for non-responders based on the results of the SEE and according to response status at week 24	[redacted]	[redacted]	£28,896

Abbreviations: BSC: best supportive care; EAG: external assessment group; ICER: incremental cost-effectiveness ratio; SEE: structured expert elicitation.

Other considerations

Equality considerations

- Disease assessment tools may underestimate disease severity in people with darker skin
- Prurigo nodularis is more prevalent in people of south and east Asian family background in the UK who are more likely to have severe eczema and prurigo nodularis.
- A study in the United States reported a higher prevalence of prurigo nodularis in people of African and African Caribbean family background.
- Prurigo nodularis presents more frequently in women.

Severity

- Company consider dupilumab is not expected to meet the severity modifier criteria

Innovation

- No additional benefits not captured in the modelling

NICE National Institute for Health and Care Excellence

Thank you.