Single Technology Appraisal

Dupilumab for treating prurigo nodularis [ID4054]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dupilumab for treating prurigo nodularis [ID4054]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Sanofi:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. British Association of Dermatologists
   b. Prurigo Nodularis International

4. **External Assessment Report** prepared by York

5. **External Assessment Report – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dupilumab for treating prurigo nodularis [ID4054]

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Abbreviations

Abbreviation	Definition
AD	Atopic dermatitis
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
BOI	Burden of illness
BSA	Body surface area
BSC	Best supportive care
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPRD	Clinical Practice Research Datalink
CRSwNP	Chronic rhinosinusitis with nasal polyps
DAS	Deterministic sensitivity analyses
DLQI	Dermatological Life Quality Index
EADV	European Academy of Dermatology and Venereology
EAG	External assessment group
EPP	European Prurigo Project
EQ-5D	EuroQol five-dimensions
EQ-5D-5L	EuroQol five-dimensions five-levels
GP	General practitioner
HADS (A/D)	Hospital Anxiety and Depression Scale (anxiety/depression subscale)
HES	Hospital Episode Statistic
HCRU	Healthcare resource use
HRQoL	Health-related quality of life
HUI3	Health Utilities Index Mark 3
ICER	Incremental cost-effectiveness ratio
IFSI	International Forum for the Study of Itch
IGA	Investigator Global Assessment
IGA PN (-A/S)	Investigator's Global Assessment for Prurigo Nodularis (– Activity/Stage)
IL	Interleukin
IMP	Investigational medicinal product
ITT	Intent-to-treat
LS	Least squares
MI	Multiple imputation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRS	Numerical Rating Scale
OLE	Open-label extension
OR	Odds ratio
PAS	Prurigo Activity Score
PN	Prurigo nodularis
PPY	Per patient year
PPPY	Per patient per year
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
SAE	Serious adverse events

Abbreviation	Definition
SD	Standard deviation
SEE	Structured expert elicitation
SLR	Systematic literature review
SoC	Standard of care
STEER	Structured expert elicitation resources
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment emergent adverse event
TLR	Targeted literature review
UK	United Kingdom
US	United States
UV	Ultraviolet
VAS	Visual Analogue Scale
WI-NRS	Worst-Itch Numeric Rating Scale
WTP	Willingness-to-pay

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

B.1.1 Decision problem

This single technology appraisal evaluates the clinical- and cost-effectiveness of dupilumab as a treatment option for moderate-to-severe prurigo nodularis (PN). Dupilumab is licensed for the treatment of adults with moderate-to-severe PN who are candidates for systemic therapy in the UK.

The final scope for dupilumab for PN was issued by National Institute for Health and Care Excellence (NICE) in November 2022.The key evidence in this submission is based on the results of PRIME2 and PRIME, two replicate phase III randomised controlled trials (RCTs) that evaluated the efficacy and safety of dupilumab versus best supportive care (BSC) in patients with PN. The decision problem addressed in this submission is summarised in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
Population	Adults with moderate-to-severe PN that had inadequate response or intolerance to existing topical treatments	As per final scope	N/A
Intervention	Dupilumab in combination with topical emollients, TCSs and TCIs	As per final scope	N/A
Comparator(s)	Established clinical management without dupilumab, including: • Topical emollients • TCS • TCI • Antihistamines • Oral steroids • Phototherapy • Immunosuppressive therapies (azathioprine, cyclosporin, methotrexate or thalidomide)	The company considers the following comparators to be the most relevant: • Topical emollients • TCS • TCI	There is a lack of RCT evidence to support the efficacy of antihistamines, oral steroids, phototherapy, immunosuppressive therapies and antidepressants in treatment of PN. Phototherapy is used earlier in the treatment pathway and so cannot be regarded as a direct comparator. Moreover, clinical experts in the UK who participated in the December 2022 advisory board conducted by Sanofi advised positioning dupilumab where off-label systemics are currently used to provide patients with the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Antidepressants including SSRIs and SNRIs		most effective treatment as early as possible while minimising potential side effects.(1)
Outcomes	The outcome measures to be considered include: • Measures of disease severity • Measures of symptom control including improvement in itch • Disease-free period/maintenance of remission • Time to relapse/prevention of relapse • Adverse effects of treatment • HRQoL	Outcomes measured in PRIME2 and PRIME: • Measures of disease severity • Measures of symptom control including improvement in itch • Adverse effects of treatment • HRQoL	Disease-free period/maintenance of remission and time to relapse/prevention of relapse outcomes were included in the scope to align with a previous submission to NICE for AD [TA534](2); however, these outcomes are not relevant to PN.

AD = atopic dermatitis; HRQoL = health-related quality of life; N/A = not applicable; NICE = National Institute for Health and Care Excellence; PN = prurigo nodularis; RCT = randomised controlled trial; SNRI = serotonin-norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids

B.1.2 Description of the technology being evaluated

A description of dupilumab, the technology being appraised, is presented in Table 2. The Summary of Product Characteristics for dupilumab can be found in Appendix C.(3)

Table 2. Technology being evaluated

UK approved name and brand name	Dupilumab (Dupixent®)
Mechanism of action	Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling.(3) Dupilumab inhibits IL-4 signalling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signalling through the Type II receptor (IL-4Rα/IL-13Rα). IL-4 and IL-13 are major drivers of human type 2 inflammatory disease, such as AD, asthma and CRSwNP. Blocking the IL-4/IL-13 pathway with dupilumab in patients decreases many of the mediators of type 2 inflammation.(3)
Marketing authorisation/CE mark status	EMA marketing authorisation approval for dupilumab in adults with moderate-to-severe PN was received on 12 December 2022.(3) The Type II variation to extend the approved indication for dupilumab to include treatment of adults with PN received MHRA approval for Great Britain on 14th February.
Indications and any restriction(s) as described in the summary of product characteristics	Dupilumab is indicated for the treatment of adults with moderate-to-severe PN who are candidates for systemic therapy.(3)

Method of administration and dosage	The recommended dose of dupilumab for adult patients is an initial dose of 600 mg (two 300 mg injections administered in different injection sites), followed by 300 mg given every other week.(3) Dupilumab is self-administered by SC injection into the thigh or abdomen, except for the two inches (five cm) around the navel, using a single-use pre-filled syringe or pen. If the injection is being administered by somebody else, the upper arm can also be used.(3)
Additional tests or investigations	No additional tests beyond those already recommended for patients with PN are required
List price and average cost of a course of treatment	£1,264.89 per pack £16,500 PPPY
Patient access scheme (if applicable)	[redacted] In addition to the simple discount patient access scheme, dupilumab is eligible for VPAS payments. This represents an additional 26.5% rebate on net sales of the product in 2023.

AD = atopic dermatitis; CRSwNP = chronic rhinosinusitis with nasal polyps; EMA = European Medicines Agency; IgG = Immunoglobulin G; IL = interleukin; MHRA = Medicines and Healthcare products Regulatory Agency; PN = prurigo nodularis; PPPY= per patient per year; SC = subcutaneous; UK = United Kingdom; VPAS = voluntary scheme on branded medicines

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

Disease overview and burden

- PN is a chronic, recalcitrant, inflammatory, neural and immune-mediated skin disease, characterised by nodular lesions and intense pruritus.(4-9)
- PN has a prevalence of 3.27 per 10,000 in England and is considered a rare disease; 26.8% of the patients with PN have moderate-to-severe inadequately controlled disease.(10-13)
- Patients with PN experience a range of debilitating symptoms including itch, skin lesions, pain, depression and anxiety.(8, 14)
- All aspects of patients' lives and mental health are affected, leading to reduced participation in activities, decreased productivity and substantial healthcare resource use (HCRU).(15-17)

Clinical pathway of care

- There is a lack of established diagnostic and treatment guidelines for PN and limited supportive evidence from RCTs to support decision-making.(4, 5, 18-20)
- The 2020 International Forum for the Study of Itch (IFSI) guidelines for the treatment of chronic prurigo, including PN, in adults recommended emollients, topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), intralesional corticosteroids, ultraviolet (UV) phototherapy and systemic therapies (including immunosuppressants and antidepressant treatments) for patients with PN (21); however, there is no well-defined BSC for PN in the UK.(1)

Unmet need

- There are no approved targeted systemic treatments for PN aside from dupilumab.(4, 5, 19)
- All currently prescribed off-label and non-targeted systemic therapies lack supporting RCT evidence and are associated with safety and tolerability concerns.(16, 18, 20, 22-26)
- There is an unmet need for efficacious, targeted, systemic therapies for PN that reduce itching, contribute to the resolution of skin lesions, improve health-related quality of life (HRQoL) and have a favourable risk-benefit profile.(15)

Proposed positioning of dupilumab

- It is anticipated that dupilumab will be used in combination with topical emollients, TCSs and TCIs in patients with moderate-to-severe PN whose disease is inadequately controlled with topical prescription therapies or when those therapies were not advisable.

B.1.3.1 Disease overview

B.1.3.1.1 Disease background

PN is a chronic, recalcitrant, neural and immune-mediated skin disease driven in part by persistent underlying type 2 inflammation.(4-6, 9) PN is the most well-known subtype of chronic prurigo and can persist for many years; the disease is characterised by nodular lesions and inflammation, which are perpetuated by a cycle of itching and scratching. These manifestations in turn contribute substantially to disease burden (Section B.1.3.1.6).(7, 8)

While disease pathophysiology remains incompletely understood, PN is believed to be the phenotypic manifestation of a range of different underlying conditions mediated by increases in interleukin-4 and -13 (IL-4 and IL-13), which are key drivers of type 2 inflammation and chronic itch sensitisation.(19, 20, 27) IL-4 and IL-13 are associated with production of IL-31, which induces itching and scratching in patients with PN.(28) Several investigations have indicated that a combination of pro-inflammatory and pruritogenic molecules result in the release of neuropeptides such as calcitonin-gene related peptide and substance P, which contribute to inflammation and sensory dysfunction.(6, 19)

B.1.3.1.2 Clinical presentation

PN is a distinct dermatological disease characterised by crusted or excoriated, hyperkeratotic (i.e., thickening of the outer layer of the skin) nodules or lesions*, which may

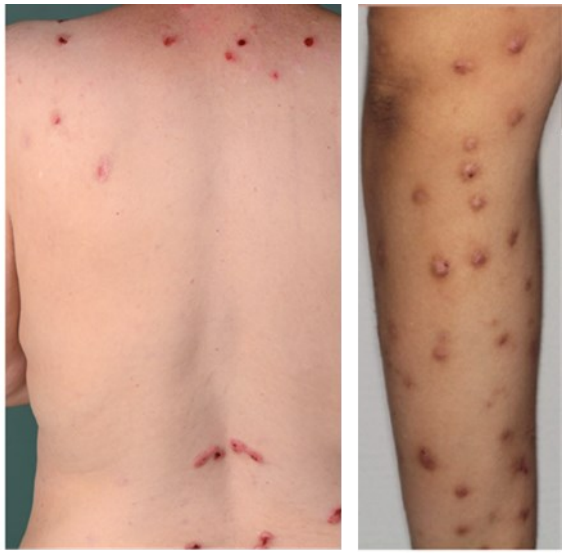
* 'Nodules' and 'lesions' are interchangeable terms

itch or bleed.(5, 7, 8) A hyperpigmented border is frequently observed around the outside of lesions which are whitish or pink (Figure 1).(7, 29)

Based on a retrospective study on the clinical presentation of PN in Germany, which is expected to be representative of patients with PN in United Kingdom (UK) clinical practice, most patients (68.5%) present with localised PN at disease onset but 56.5% progress to generalised PN over the disease course.(30) PN lesions are usually distributed symmetrically across areas that are easily scratched, such as the arms and legs, and 49% of patients have three to four affected areas.(15, 20, 31)

Itching and scratching (which can be continuous or sporadic) and skin lesions are the most commonly reported and burdensome symptoms (see Section B.1.3.1.6 for further details on disease burden).(8, 30) Other common symptoms include skin burning, stinging and tingling sensations, sleep disturbances and psychological distress.(15, 30, 32) Less commonly reported symptoms include changes in temperature (hot and cold) and prickling, sharp, stroking and electrical sensations.(15, 30, 32)

Figure 1. Clinical presentation of PN(29)



PN = prurigo nodularis
Source: Sanofi. Data on file. NHS England Commercial Surgery Dupixent. 2022.

B.1.3.1.3 Diagnosis

Diagnosis of PN in the UK can be a long process due to a lack of awareness among general practitioners (GPs) about what PN is and misdiagnosis of PN as a different disease. A patient testimony from an interview with a PN patient conducted by Sanofi in October 2022 highlights the challenges with patient access to appropriate medical care.(14) In particular,

the patient made the following comments about the time it took to receive a correct diagnosis and lack of clinician follow-up:(14)

- '**Nobody really supported me** in my journey with nodular prurigo because I haven't had a follow-up appointment yet.'
- 'My nodular prurigo was initially diagnosed as cellulitis when I became unwell with Lyme Disease which presented as extreme joint pain and lots of skin issues. Eventually **after about nine years of this I was referred to a dermatologist** because it wasn't cleared up by antibiotics.'
- 'After my initial diagnosis [of PN] in 2020 at the start of the pandemic, **I was just left to deal with it**. My diagnosis was given over the phone and three follow-up appointments have been cancelled due to COVID. We're two years down the line and because of COVID-19 I've been in limbo.'

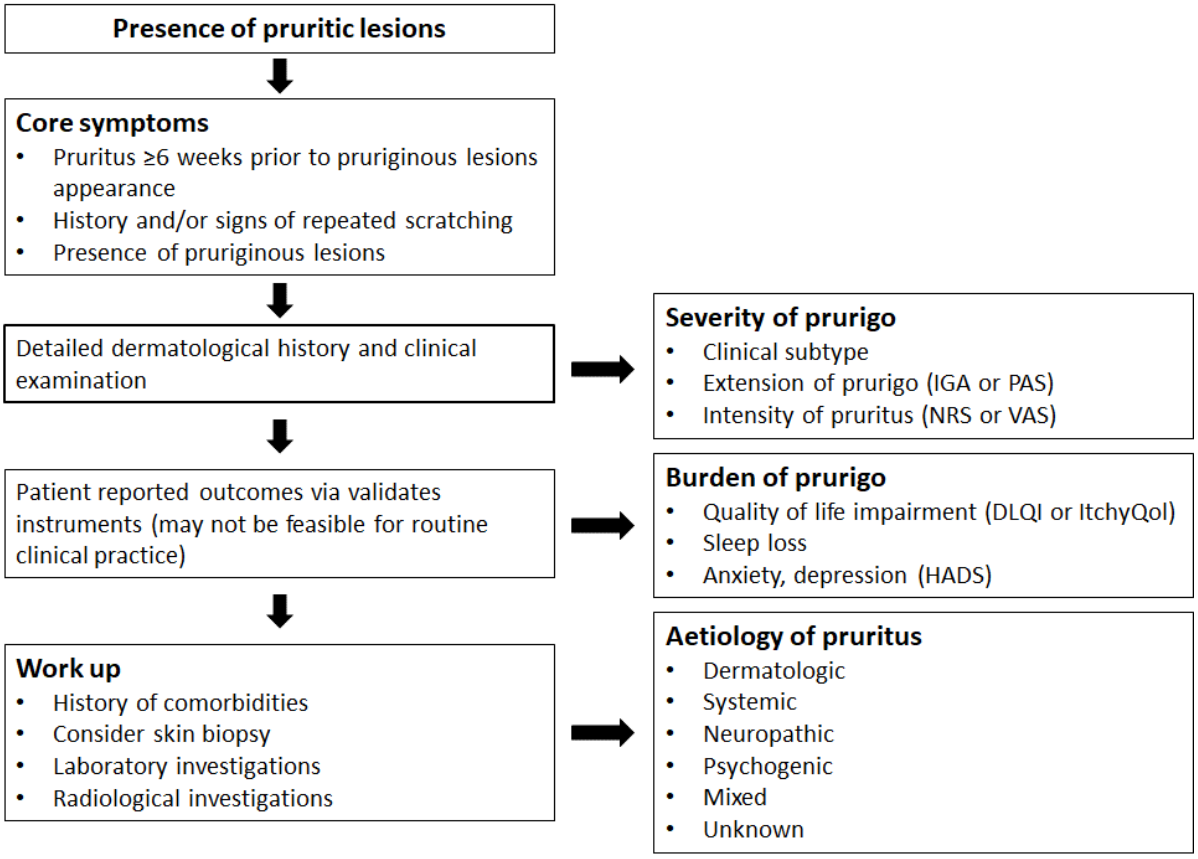
In the absence of established diagnostic guidelines specifically for PN in the UK, a group of clinicians in Germany and the United States (US) proposed a diagnosis algorithm for PN in 2020 based on clinician experience and RCTs to standardise disease management across geographical regions.(20) The proposed algorithm is presented in Figure 2 and the diagnostic steps are summarised as follows:

- Initial medical history evaluation and skin examination to identify patients with PN based on symptoms.
- Detailed dermatological history of pruritus and clinical examination to evaluate local and systemic disease.
- Assessment of the severity and extent of PN, using the Prurigo Activity Score (PAS) and/or a reflective Investigator Global Assessment (IGA), Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), as well as the burden of PN on patients via validated surveys on HRQoL (e.g., Dermatological Life Quality Index [DLQI] or ItchyQoL) and emotional status (e.g., Hospital Anxiety and Depression Scale [HADS], Hamilton Depression Rating Scale).
- A complete workup might be necessary to highlight potential causes of PN (e.g., history of comorbidities, skin biopsy, blood and radiological test).

In accordance with the above proposed diagnostic algorithm, the British Association of Dermatologists patient leaflet on PN includes itching and the typical PN skin lesions (hard lumps with rough, thick surface, surrounded by darker skin) as adequate requirements for diagnosis.(33) If case diagnosis based on clinical presentation is inconclusive, skin biopsy and blood tests to exclude other itch-inducing conditions are recommended.(33) UK dermatologists have confirmed that there is currently no established scoring system for evaluating the severity of PN.(1, 34) However, UK clinicians who participated in an advisory

board conducted by Sanofi in December 2022 expressed a willingness to assess PN based on extension of prurigo and intensity of pruritus in future clinical practice.(1)

Figure 2. Diagnosis algorithm for chronic PN proposed by international clinicians(20)



DLQI = Dermatology Life Quality Index; HADS = Hospital Anxiety and Depression Scale; IGA = Investigator Global Assessment; NRS = Numerical Rating Scale; PAS = Prurigo Activity Score; PN = prurigo nodularis; VAS = Visual Analogue Scale.
Source: Adapted from Ständer et al. 2020.

B.1.3.1.4 Disease staging

Few studies have been published on disease staging in PN. The diagnostic and treatment algorithm published by German and US clinicians in 2020 recommended considering both the extent and intensity of symptoms when assessing disease severity.(20) One method of staging uses the Investigator's Global Assessment for Prurigo Nodularis – Stage (IGA PN-S) scale, in which investigators assess disease severity and classify patients on a five-point scale ranging from 0 (clear) to 4 (severe):(20)

- **Grade 0 (clear):** no nodules (zero nodules)
- **Grade 1 (almost clear):** rare, flattened lesions, with no more than five dome-shaped palpable nodules (approximately one to five nodules)
- **Grade 2 (mild):** few, mostly flattened lesions, with small number of dome-shaped palpable nodules (approximately six 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)

The PAS questionnaire can also be used to assess the type, number and distribution of lesions along with the affected areas and the proportion of healed lesions relative to excoriated lesions.(20) The intensity of pruritus is scored from 0 (best) to 10 (worst) and severity is categorised as no pruritus (0), mild/low intensity pruritus (>0 to <three), moderate pruritus (≥three to <seven), severe pruritus (≥seven to <nine) or very severe pruritus (≥nine).(20)

Disease severity classification for PN was also assessed in the qualitative UK dermatologist interviews conducted by Sanofi.(34) Respondents defined mild PN as one or two lesions and severe PN as more than two lesions or '*thicker*', more callous lesions, although they confirmed that there is no established scoring system for severity.(34)

B.1.3.1.5 Epidemiology

Prior to 2022, there were no published studies investigating the prevalence of PN in the UK. UK clinicians who participated in an advisory board conducted by Sanofi in December 2022 highlighted the difficulty of studying the PN population due to under-referral of patients with PN.(1) Moreover, patients who do not respond to treatment were noted to '*jump from department to department…constantly moving and giving up*'.(1)

To address this data gap, Morgan et al. 2022 conducted a database analysis of 2,416 patients with a documented diagnosis of PN between 2008 and 2018 in the Clinical Practice Research Datalink (CPRD) Aurum database, which contains primary care data from over 40 million patients in the UK.(11) The mean (standard deviation [SD]) age of first recorded diagnosis was 61.1 years (18.4) and a higher proportion of patients were female (58.9%).(11) The estimated point prevalence of PN in England was 3.27 (95% confidence interval [CI]: 3.15, 3.40) per 10,000 in 2018.(11) This makes PN a 'rare disease' under the UK Rare Diseases Framework definition: '*a condition which affects less than 1 in 2,000 people*'.(10) The total number of patients with PN in England was estimated to be 18,471 in 2018.(11) The incidence of PN between 2008 and 2018 was 2.88 (95% CI: 2.77, 3.00) per 100,000 patient years.(11)

Sanofi also conducted a study utilising the CPRD Aurum and Gold databases linked to Hospital Episode Statistics (HES) in England examining patient records between 2007 and

2019.(35, 36) A manuscript reporting the results for this study is currently under review for publication.

- This identified 8,933 patients with PN, of which 2,498 patients (28%) required systemic treatment and were therefore classified as having moderate-to-severe disease.(35) Patient demographics reported in this study were similar to the Morgan et al. 2022 study (mean age: 61 years; females: 57%).(35)
- The incidence of PN was 9.31 per 100,000 and the incidence of moderate-to-severe PN was 3.23 per 100,000 in 2019.(35) The estimated prevalence of PN and moderate-to-severe PN was 8.8 per 10,000 and 1.89 per 10,000, respectively.(35)
- While the Morgan et al. 2022 study included only patients with two distinct PN diagnoses to avoid false positives due to patients with diagnoses recorded for exploratory investigation, the Sanofi study included patients with a single diagnosis of PN.(11, 35) Therefore, the Morgan et al. 2022 study is considered a more conservative estimate of PN epidemiology in England and 3.27 per 10,000 is used as the base-case prevalence for the purpose of this submission.(11)

The proportion of patients with moderate-to-severe and inadequately controlled PN (defined as patients who did not respond to first-line treatment [topical steroids and antihistamines]) is estimated to be 26.8% of the PN adult population in the UK.(12, 13) Based on a prevalence of 3.27 per 10,000 and a predicted English population of 45,107,158 individuals aged ≥18 years at the end of 2023 (per Office for National Statistics projections(37, 38)), we estimate there are currently 14,750 adult patients with PN and 3,953 adult patients with moderate-to-severe and inadequately controlled PN in England.(11)

B.1.3.1.6 Disease burden

B.1.3.1.6.1 Clinical burden

Patients with PN experience a range of persistent symptoms that can vary in extent and severity, with itch being the most frequently reported and the most burdensome symptom.(8) In the European Prurigo Project (EPP), 71.1% of patients with PN reported often or always experiencing disease symptoms, 53.1% said itch always or often impacted everyday life and 49.3% reported the highest burden being associated with itch (N=509).(8) Following itch, patients included in the EPP reported visibility of skin lesions (21.4%) and bleeding of skin lesions (14.1%) to be the most burdensome aspects of PN.(8)

Itch was described as '*disturbing*' (55.2%), '*burdensome*' (50.7%), '*agonising*' (46.6%), '*intractable*' (35.0%), '*itching*' (22.4%), '*aggression inducing*' (21.7%), '*cruel*' (18.2%), '*beastly*' (17.0%) and '*horrendous*' (15.0%) by patients in the EPP.(8) This is concordant with results from a Sanofi study in which interviews were conducted with 12 dermatologists and five PN patients in the UK; itch was described as the most defining and impactful symptom

of PN by clinicians and patients.(17, 34) Patients interviewed by Sanofi also noted the burden of PN nodules, which cause *'a lot of pain'* when scratched, prevent patients from getting comfortable during sleep and reduce patient participation in physical activities due to self-consciousness.(14, 17) One patient described the pain associated with PN as *'intense'*, *'like sticking a hot needle in your skin'* and highlighted scratching of nodules to relive itch as an action that *'makes the pain worse'*.(14) Clinicians interviewed by Sanofi highlighted the impact of itch on sleep, depression and/or anxiety and long-term scars.(17, 34)

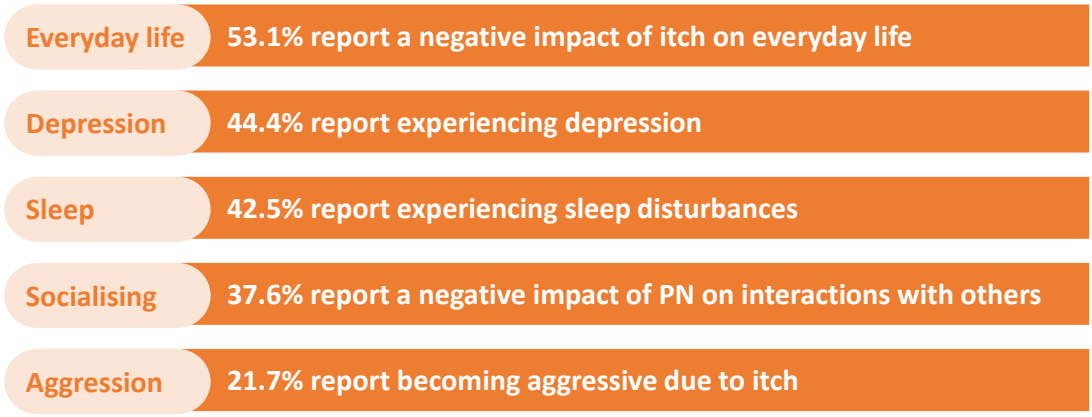
B.1.3.1.6.2 Humanistic burden

The lived experience of patients with PN is one of significant impact across all aspects of their lives, including work, sleep, exercise, clothing, travel and holidays, relationships with family and partners, self-esteem and mental health.(17) A patient with PN in the UK interviewed by Sanofi in 2022 noted *"living with nodular prurigo[†] affects my daily schedule all the time. It's not something I forget about, it's always there. I'm always aware of what my skin looks like to other people, so there's always an effect."* and described anxiety and depression associated with PN as a *'circle of hate'* due to being *'anxious about going out because I don't like people looking at my skin'* and being depressed *'because I don't go out because of my skin'*.(14)

More than half of patients in the EPP described above (53.1%) felt itching had a '*very negative*' or '*rather negative*' impact on everyday life and 37.6% of patients felt PN symptoms had a '*very negative*' or '*rather negative*' impact on interactions with others, with 21.7% of patients becoming aggressive due to itch.(8) Moreover, patients with PN often experience depression and sleep disturbances (Figure 3).(8) Additional studies conducted in Europe (including the UK) have reported significantly higher frequency of depression and anxiety in patients with PN compared to controls without PN ($p<0.001$ for both).(39, 40)

[†] N.B., PN and nodular prurigo are interchangeable terms and 'PN' is used for the majority of this submission. In this instance 'nodular prurigo' is used as a direct patient quote.

Figure 3. Humanistic burden of PN(8)



PN = prurigo nodularis

Analyses of the specific humanistic burden of skin lesions were not identified in the literature. Nevertheless, as noted above, both patients in the EPP and clinicians from the European Academy of Dermatology and Venereology (EADV) frequently list skin lesions as a significant factor that negatively affects daily living.(8, 15)

Given the EuroQoL five-dimensions (EQ-5D) is a generic measure of HRQoL that may not fully capture the impact of PN on everyday life, the dermatology-specific DLQI is considered a more appropriate measure of humanistic burden in patients with PN.(41)

In a prospective observational study of 552 patients with various common dermatological diseases in Europe, mean DLQI score was higher in patients with PN (11.6) than in patients with atopic dermatitis (AD; 10.7) and psoriasis (10.6), indicating worse HRQoL in patients with PN.(42) Patients with PN also reported significantly greater itch intensity than patients with AD and psoriasis ($p<0.05$ for both comparisons).(42) HADS-assessed depression and anxiety have been reported more frequently in patients with PN than in patients with hand eczema, atopic eczema, psoriasis and leg ulcers in Europe,(40) and a US survey reported poorer Pittsburgh Sleep Quality Index-assessed sleep quality in patients with PN than in patients with AD and psoriasis.(43)

A carer for a patient with PN who was interviewed by Sanofi in 2022 described the experience of being physically unable to do anything to stop the patient's pain as 'upsetting'.(44) PN was also noted to have a 'major impact' on social activities together and the carer described PN as 'frustrating' and 'challenging' from a mental health perspective.(44)

B.1.3.1.6.3 Economic burden

PN is associated with decreased productivity due to absence from work and/or early retirement and substantial HCRU, which is largely attributable to outpatient care.(15, 16) In the series of qualitative interviews with 12 UK dermatologists conducted by Sanofi, 80% of patients with severe PN were estimated to require secondary care.(34) Dermatologists also highlighted the complexity and frequency of consultations required for patients with PN (review every two to three months [or four to six visits per year] for two to three years).(34)

In the retrospective analysis of CPRD Aurum and Gold databases linked to HES in England conducted by Sanofi, 99.4% of patients in the overall PN population required at least one GP visit per year (Table 3). In addition, the mean number of annual GP visits per patient was 14.27 (N=8,933).(36) The majority of patients in the overall PN population required at least one outpatient visit (93.1%) or accident and emergency visit (68.1%) once per year. Moreover, patients with a coding for PN in their medical record experienced a mean number of 6.68 outpatient visits with any speciality per year. Dermatology inpatient stays occurred in 7.8% of patients with PN at least once per year, and over half of inpatient stays were PN-specific (4.6%).(36) Results from this study were presented at ISPOR EU 2022 and will be published in a manuscript later in 2023.(36) Costs and HCRU in patients with moderate-to-severe PN are presented in Section B.3.5.

Table 3. All-cause HCRU in the overall PN population in England (N=8,933)(36)

	Number of patients with a visit (%)	Mean rate of visit, PPPY (95% CI)
GP visits	8,883 (99.4)	14.27 (14.24, 14.31)
Outpatient visits (any specialty)	8,312 (93.1)	6.68 (6.66, 6.71)
Inpatient hospitalisation (dermatology)	697 (7.8)	0.04 (0.04, 0.04)
Inpatient hospitalisation (PN specific – primary)	409 (4.6)	0.02 (0.02, 0.02)
A&E visits	6,080 (68.1)	0.63 (0.62, 0.63)

A&E = accident and emergency; CI = confidence interval; GP = general practitioner; HCRU = healthcare resource use; PN = prurigo nodularis; PPPY = per patient per year

B.1.3.2 Clinical pathway of care and dupilumab place in therapy

B.1.3.2.1 Current treatment options in the UK

Successful treatment of PN is challenging due to the absence of approved or licensed targeted systemic therapies (aside from dupilumab), the lack of established treatment guidelines for PN and the limited supportive evidence from RCTs to support decision-making.(4, 5, 18-20) Based on the results of an advisory board conducted by Sanofi in December 2022 with UK clinicians who treat patients with PN, there is no well-defined BSC for patients with PN.(1)

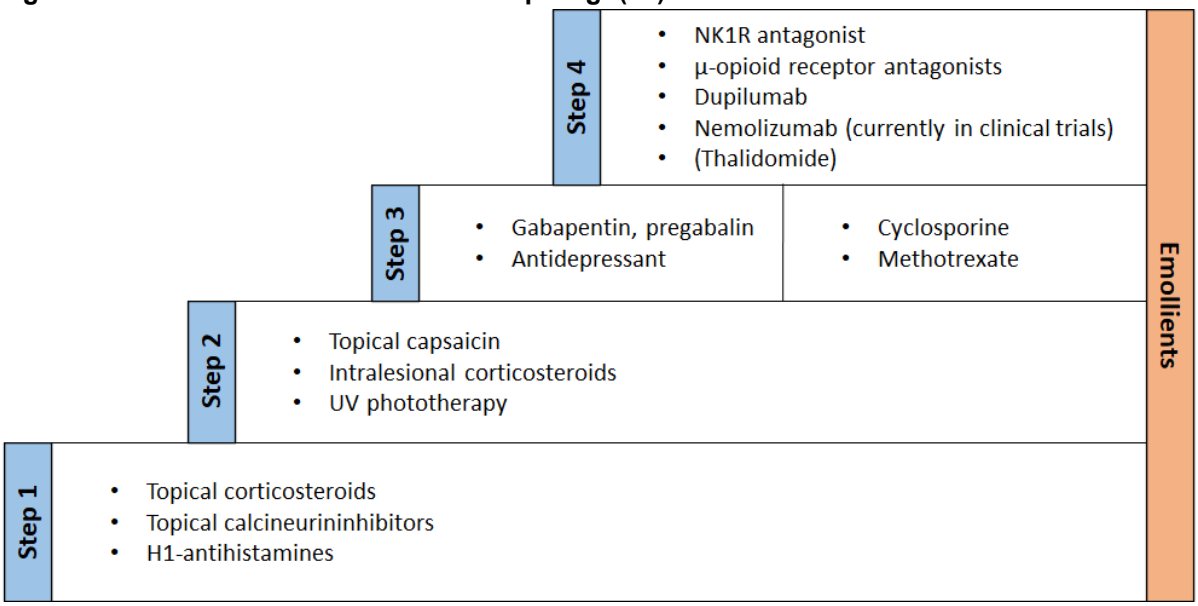
In 2020, the IFSI published guidelines for chronic prurigo, including PN, in adults (Figure 4).(21) These guidelines recommend a step-wise, multi-modal treatment approach to control pruritus, treating the potential cause of pruritus and healing the pruriginous lesions; based on expert opinion and available RCT data.(21) The main therapeutic modalities recommended are:(21)

- Topicals, including TCS and TCI
- Intralesional corticosteroids
- UV phototherapy
- Systemic therapies, including immunosuppressants and antidepressant treatments

The use of emollients as supportive care is also advised throughout the treatment course.(21) While antihistamines are acknowledged as a 'widely used' treatment option in chronic prurigo, the IFSI guidelines note that evidence of an antipruritic effect is 'low' and do not recommend use of antihistamines as a monotherapy for longer than four weeks.(21) This is supported by the results of a clinician survey, where 30 EADV members unanimously agreed that antihistamines are generally ineffective for treating PN.(15) The British Association of Dermatologists and British Photodermatology Group guidelines for UV phototherapy published in 2022 also suggest that the evidence base for use of phototherapy in PN is weak.(45)

Overall, very few RCTs and placebo-controlled studies have been conducted in patients with PN; the majority of recommendations in the IFSI guidelines are based on moderate, low or very low quality evidence from case series and case reports.(21) This indicates that current recommendations are likely to be changed by further research.(21) A combination of treatments across steps can be used and personalised therapeutic plans should be tailored to the patient's age, comorbidities, PN severity, HRQoL, treatment history and associated side effects.(4, 5, 19, 21)

Figure 4. IFSI treatment ladder in chronic prurigo(21)



IFSI = International Forum for the Study of Itch; NK1R = neurokinin-1 receptor; UV = ultraviolet
Source: Adapted from Ständer et al. 2020

The IFSI guidelines are generally aligned with treatment practices reported by members of the EADV in 2018 and with consensus recommendations made by US dermatology experts in 2020.(15, 46)

- Of the 30 EADV members‡ who responded to a survey about diagnosis and management of PN, the majority reported prescribing antihistamines (90.0%), antidepressants (90.0%), gabapentinoids (86.7%) and immunosuppressants (86.7%) to patients with PN, despite all respondents agreeing antihistamines are 'generally ineffective for PN-associated pruritus'.(15) Moreover, antidepressants are considered an adjunct therapy for chronic itch and respondents generally agreed they are not effective for treating PN.(15, 47)
- Similarly, the US treatment ladder includes TCS, TCI, topical capsaicin, gabapentinoids, antidepressants, phototherapy and immunosuppressants, but do not recommend antihistamines because they are unlikely to be effective.(46)

Based on a series of qualitative interviews with 12 dermatologists and quantitative interviews with 50 dermatologists conducted by Sanofi in 2020, the treatment pathway for PN in the UK is consistent with IFSI recommendations, EADV treatment practices and US consensus recommendations.(17, 34)

- In clinical practice, 31% of patients only go as far as Step 1 treatment with high-dose topical steroids, general emollients, antihistamines, capsaicin and/or menthol.(17)

‡ Survey respondents were from Austria, Finland, France, Germany, India, Italy, Norway, Poland, Portugal, Russia, Spain, Sweden, Turkey and the UK

- An estimated 30% would receive Step 2 treatment with phototherapy, gabapentin, antidepressants, steroid injection, cryotherapy and/or surgery after Step 1 treatments.(17) However, 64% of dermatologists noted 29% of patients move directly from Step 1 to Step 3.(17)
- A further 30% would receive Step 3 treatment with methotrexate, cyclosporin and/or azathioprine.(17)
- The final 9% would receive Step 4 treatment with thalidomide or another treatment.(17)

Patients may receive up to four or five different treatments per treatment stage.(17) The majority of interviewed clinicians described PN as a '*really challenging and frustrating condition to treat*'.(34) Overall, 28% of patients with PN never achieve disease control despite reaching Step 3 or 4 treatment.(34)

B.1.3.2.2 Limitations of current treatment options

The multi-factorial aetiology of PN requires multi-modal treatment and long-term management, including both topical and systematic therapies, to achieve pruritic relief and healing of PN lesions.(19, 20) However, no approved targeted systemic treatments for PN exist aside from dupilumab and there is a lack of RCT evidence to support currently used off-label treatment regimens and associated outcomes.(4, 5, 19) While phototherapy can be a useful treatment in patients with PN who have limited options (e.g., due to comorbidities or drug interaction with other medications),(48) it is not always considered appropriate by UK clinicians and the majority of patients who receive phototherapy do not achieve a complete response.(17, 49) Limited availability means phototherapy is not universally accessible,(45) and travelling to a centre that provides phototherapy may be inconvenient for patients due to the frequency of sessions (typically three per week).(50) Thus, it is unclear whether phototherapy can be considered standard of care.

Symptom resolution for patients with PN can take months and evidence on the effectiveness of off-label treatments is mostly limited to non-randomised studies with small patient populations.(16, 20, 24) Moreover, patients with PN in the UK have reported antihistamines do not *'make the itching go away completely'* despite taking *'a prescription antihistamine at night-time on most days'*.(14)

All currently prescribed off-label treatments are associated with adverse events (AEs):(16, 20)

- Commonly used topical treatments such as TCS and UV phototherapy are associated with local site reactions (including burning, itching, irritation and dry skin) and UV erythema, respectively.(16, 18, 20, 22, 23)

- Off-label systemic therapies can be associated with serious AEs that include peripheral oedema (gabapentinoids) and renal dysfunction (immunosuppressants).(20)
- Increased risk of malignancy has been reported in patients treated with methotrexate, cyclosporine and azathioprine.(24)
- Several off-label systemic therapies are contraindicated for patients with comorbidities affecting liver and renal function (e.g., μ-opioid receptor antagonists, cyclosporine and methotrexate).(20, 25, 26) In particular, changes in hepatic and renal function are common AEs associated with long-term use of cyclosporin.(24)

In a prospective, cross-sectional, cohort study in Europe, 56.8% of patients were unsatisfied with the therapy they had received in the previous six months and 28.7% of patients did not consider any of the current treatment options effective.(23) Treatments used by patients in this study included emollients, topical steroids, antihistamines, UV therapy, systemic immunosuppressants, antidepressants, gabapentin/pregabalin, topical immunomodulators and psychotherapy.(23)

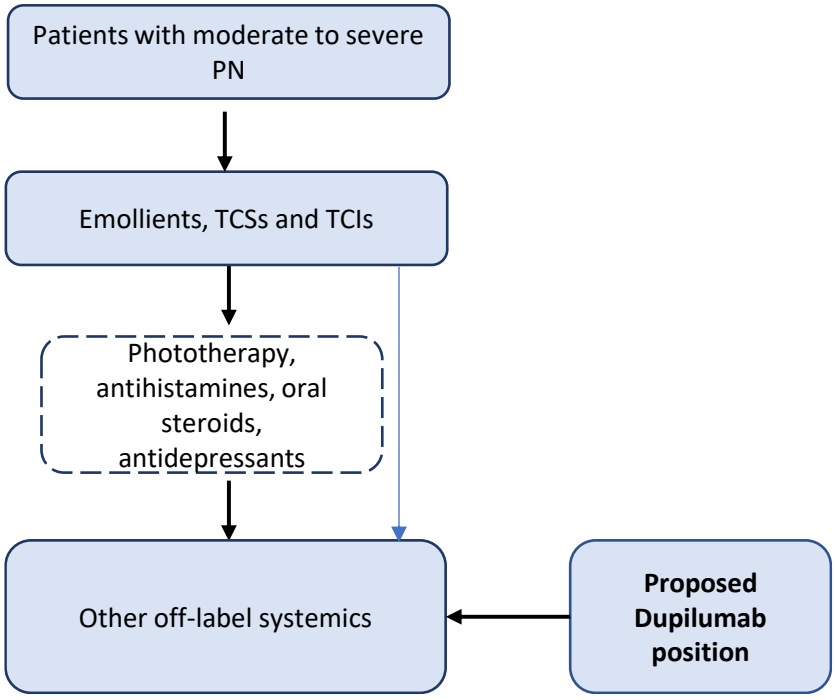
B.1.3.2.3 Proposed positioning of dupilumab

There are currently no licensed systemic therapies for the treatment of PN aside from dupilumab, which is currently licenced in the UK (February 2023) and the EU (December 2022). Dupilumab will be indicated for the treatment of adults with moderate-to-severe PN who are candidates for systemic therapy in the UK during the course of this NICE evaluation.(3) The recent EADV consensus recommendations highlighted the substantial unmet need for efficacious, targeted, systemic therapies with a favourable risk-benefit profile that address the multi-modal aetiology of PN.(15) Patients require a treatment option that reduces itching, decreases the number of nodules and improves HRQoL with minimal side effects. The phase III PRIME2 and PRIME trials have demonstrated that dupilumab can address these important clinical and patient treatment goals (Section B.2.6).

The proposed positioning of dupilumab in the treatment pathway for patients with moderate-to-severe PN, which was validated during an advisory board conducted by Sanofi in December 2022 with clinical experts who treat patients with PN in the UK, is depicted in Figure 5.(1) It is anticipated that dupilumab will be used in combination with topical emollients, TCSs and TCIs in patients with PN whose disease was inadequately controlled with topical prescription therapies. Clinical experts who participated in the December 2022 advisory board advised positioning dupilumab where off-label systemics are currently used to provide patients with the most effective treatment as early as possible while minimising potential side effects.(1) Given the lack of established treatment guidelines for PN and the limited supportive clinical evidence for other off-label systemic therapies (Section B.2.1), the

most appropriate comparator for dupilumab is BSC (defined as a combination of emollients, mild-to-moderate potency TCS/TCIs and rescue therapy).

Figure 5. Clinical pathway of care for moderate-to-severe PN in the UK with proposed positioning of dupilumab(1)



PN = prurigo nodularis; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; UK = United Kingdom

B.1.4 Equality considerations

In previous appraisals for dermatology indications, the NICE committee noted that it is possible that the assessment tools for assessing the severity of the disease and the response to treatment may not be sensitive enough in patients with darker skin pigmentation.(2) Careful consideration should be given to the diagnosis and assessment of efficacy for these patients.

B.2 Clinical effectiveness

A systematic literature review (SLR) identified two high-quality clinical trials for dupilumab in the relevant patient population as defined by the NICE scope (i.e., PRIME2 and PRIME)

- PRIME2 and PRIME are replicate multi-centre, randomised, double-blind, phase III, 24-week trials of dupilumab vs. BSC in patients with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were inadvisable.(51, 52)
- The primary endpoint was the proportion of patients with Worst-Itch Numeric Rating Scale (WI-NRS) improvement (reduction) ≥4 points from baseline to Week 12 for PRIME and to Week 24 for PRIME2.(51, 52)
- The pooled analysis results from both trials are presented in this submission and have informed the economic analysis.

PRIME2 and PRIME have robustly demonstrated the efficacy of dupilumab in moderate-to-severe PN

- The proportion of patients with WI-NRS improvement was 40.5% for dupilumab vs. 19% for BSC at Week 12 (nominal p<0.0001) and 58.8% in the dupilumab group vs. 19% in the BSC group at Week 24 (nominal p<0.0001).(53)
- Patients in the dupilumab group had significantly improved IGA PN-S-assessed skin lesions compared to the BSC group from Week 8 and significantly improved IGA PN-A-assessed prurigo activity from Week 4 (p<0.05 for both).(53)
- Treatment with dupilumab resulted in a nominally significant improvement in total HADS score from baseline to Week 24 compared to BSC (least square [LS] mean difference: [redacted]).(53)

The safety profile of dupilumab is acceptable and consistent with existing safety data in patients with asthma, AD and chronic rhinosinusitis with nasal polyps (CRSwNP)

- Treatment with dupilumab was well tolerated in patients with PN in the PRIME2 and PRIME studies.(54)
- Data from PRIME2 and PRIME are generally consistent with existing safety data in patients with asthma, AD and CRSwNP, where dupilumab has favourable long-term safety and tolerability and is associated with mostly mild or moderate treatment emergent AEs (TEAEs), a low rate of treatment discontinuation and a low rate of serious TEAEs.(55-59)

Dupilumab provides sustained, clinically and statistically significant improvements to PN signs, symptoms and HRQoL while having an acceptable risk-benefit profile. Dupilumab has the potential to address the unmet need in patients with PN uncontrolled on topical prescription therapy by being the first targeted systemic therapy which also does not have any monitoring requirements.

B.2.1 Identification and selection of relevant studies

An SLR was conducted to identify all relevant RCTs describing the efficacy and safety of dupilumab and any other relevant treatments for PN. There was no lower limit on time horizon for database searches and the cut-off date for articles included in the SLR was 16th December 2022.

The SLR captured a total of seven unique RCTs reported across 12 publications and 21 unique non-RCTs reported across 21 publications. Supplementary searches conducted in Clinicaltrials.gov identified two additional RCTs, PRIME2 and PRIME, not available as peer-reviewed manuscripts.

- Of the seven RCTs that met the inclusion criteria, as defined in the PICOS table presented in Appendix D.1, six were phase II trials and one was an unspecified RCT.
- In each study, the total number of patients in each treatment arm was relatively small in size, with all studies reporting ≤127 treated patients.
- The included studies were conducted during the period 2007 to 2018 (results published between 2013 and 2022) and treatments captured in this review broadly included monoclonal antibody therapies, opioids, neurokinin-1 antagonists and topical therapies.
- Of the 21 non-RCTs that met the inclusion criteria:
- Eight were retrospective studies, six were observational studies, five were prospective studies, one was an open-label proof of concept and one was a single-arm study.
- In each study, the total number of patients in each treatment arm was relatively small in size, with all studies reporting ≤86 patients.
- The study period of the included studies was 1983 to 2020 (results published between 2004 and 2021) and treatments most frequently investigated in these studies were systemic therapies rather than topical, including thalidomide (n=7) and dupilumab (n=3).

Only the studies including comparators of interest for dupilumab in PN underwent data extraction. Full details of the SLR methodology, study selection process, inclusion and exclusion criteria and results are presented in Appendix D.1.

B.2.2 List of relevant clinical effectiveness evidence

The relevant clinical effectiveness evidence for dupilumab in PN was generated from the PRIME2 and PRIME trials, summarised in Table 4. PRIME2 and PRIME have similar designs. Both studies were multi-centre, randomised, double-blind, phase III, 24-week trials of dupilumab vs. BSC in patients with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable, conducted in multiple locations in Europe (including one site in the UK), North and Latin America and Asia (N=311 overall).(51, 52, 60)

Table 4. Clinical effectiveness evidence(51, 52)

Study	NCT04202679 (PRIME2)	NCT04183335 (PRIME)
Study design	International, multi-centre, parallel group, double-blind, randomised, placebo-controlled trial	
Population	Patients with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable	
Intervention(s)	Dupilumab	
Comparator(s)	BSC	
Indicate if study supports marketing authorisation	Yes	
Indicate if study used in the economic model	Yes	
Rationale if study not used in model	Not applicable	
Reported outcomes specified in the decision problem	Clinician-assessed efficacy outcomes • IGA PN-S • IGA PN-A Patient-reported efficacy outcomes • WI-NRS • Skin Pain-NRS Patient-reported HRQoL outcomes • DLQI • EQ-5D-5L • EQ-5D VAS Safety assessments • TEAEs • SAEs • PK / PD	Clinician-assessed efficacy outcomes • IGA PN-S • IGA PN-A Patient-reported efficacy outcomes • WI-NRS • Skin Pain-NRS Patient-reported HRQoL outcomes • DLQI • EQ-5D-5L • EQ-5D VAS Safety assessments • TEAEs • SAEs • PK / PD
All other reported outcomes	Patient-reported efficacy outcomes • HADS • Sleep NRS • PGIC • PGIS	Patient-reported efficacy outcomes • HADS • Sleep NRS • PGIC • PGIS

BSC = best supportive care; DLQI = dermatology life quality index; EQ-5D VAS = EuroQol five-dimensions visual analog scale; EQ-5D-5L = EuroQol five-dimension five-level; HADS = Hospital Anxiety And Depression Scale; HRQoL = health-related quality of life; IGA PN-A = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Activity; IGA PN-S = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Stage; NRS = numeric rating scale; PD = pharmacodynamic; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; PN = prurigo nodularis; SAE = serious adverse event; TEAE = treatment emergent adverse event; WI-NRS = worst-itch numeric rating scale

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design

PRIME2 and PRIME were of near identical design; both studies were randomised, double blind, phase III trials with a 24-week treatment period and enrolled patients with PN whose

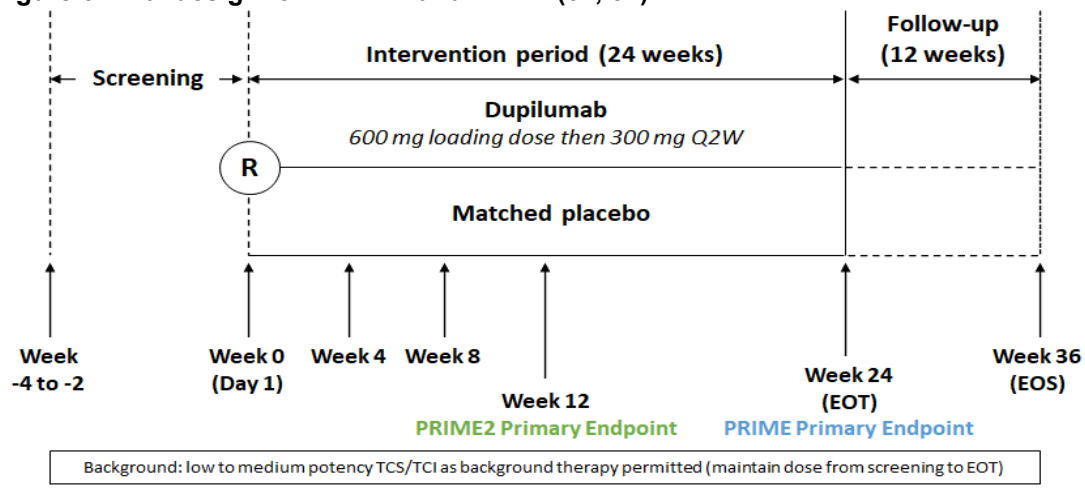
disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable.(51, 52)

The primary outcome measure for both PRIME 2 and PRIME was the proportion of patients with WI-NRS improvement (reduction) by ≥4 points from baseline:(51, 52)

- This was captured at Week 12 in PRIME2. Additionally, the proportion of patients with WI-NRS improvement (reduction) by ≥4 points from baseline at Week 24 was a key secondary endpoint of PRIME2.
- However, during the trial programme, PRIME2 results became available while PRIME was still blinded, indicating that the effect of dupilumab continually improved after Week 12.
- The study protocol for PRIME was therefore amended to make the proportion of patients with WI-NRS ≥4 from baseline to Week 24 the primary endpoint of this trial. The original primary endpoint for PRIME (i.e., proportion of participants with improvement in WI-NRS by ≥4 from baseline to Week 12) was retained but reclassified as a secondary endpoint.

The PRIME2 and PRIME studies included a screening period (two to four weeks), a 24-week treatment period and a 12-week post-treatment follow-up period (Figure 6).(51, 52)

Figure 6. Trial design for PRIME2 and PRIME(51, 52)



EOS = end of study; EOT = end of treatment; N = number of patients; Q2W = every two weeks; R = randomisation; TCI = topical calcineurin inhibitors; TCS = topical corticosteroid
Patients in both study groups were allowed to continue the use of low to medium potency TCS/TCI on stable regime without change from screening to EOT.

B.2.3.2 Patient eligibility

Eligible patients enrolled into PRIME2 and PRIME were adults aged 18 to 80 years who were diagnosed with PN at least three months before screening and for whom treatment with topical prescription therapies has failed or were not suitable for treatment with topical prescription therapies.(51, 52) Key inclusion and exclusion criteria used in the PRIME2 and

PRIME studies are summarised in Table 5.. Full inclusion and exclusion criteria are summarised in Appendix M.1.

Table 5. Selected eligibility criteria for PRIME2 and PRIME(51, 52)

Inclusion criteria
• 18 to 80 years of age • PN diagnosis by a dermatologist ≥three months before screening • Average WI-NRS score ≥7 in the seven days before Day 1 • Total ≥20 PN lesions on both legs, both arms and/or trunk, at screening and on Day 1 • Failed treatment with a two-week course of medium-to-super potent TCS or when TCS was not medically advisable • Applied of topical emollient once or twice daily for ≥five out of seven consecutive days before Day 1 • Up to 10% of atopic patients with active mild AD were allowed to be enrolled, since AD is a dermatologic condition commonly associated with PN
Exclusion criteria
• Skin morbidities (excluding PN and mild AD) that may interfere with evaluation of the study endpoints • PN (secondary) as a result of medications • PN (secondary) as a result of other medical conditions such as neuropathy or psychiatric disease • Documented moderate-to-severe AD within six months before screening or documented diagnosis of moderate-to-severe AD from screening to randomisation visit • Severe uncontrolled concomitant illnesses that, in the investigator's judgement, would adversely affect the patient's participation in the study • Active chronic or acute infection (except HIV infection) requiring treatment with systemic antibiotics, antivirals, antiprotozoals or antifungals within two weeks before screening or during the screening period

AD = atopic dermatitis; HIV = human immunodeficiency virus; PN = prurigo nodularis; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; WI-NRS = worst-itch numeric rating scale

B.2.3.3 Settings and locations where the data were collected

The PRIME study was conducted at 63 centres which screened at least one participant in eight countries/regions worldwide (US, Argentina, Mexico, Mainland China, Japan, Russian Federation, Republic of Korea and France).(51) Of these 63 centres, 58 randomised at least one participant.(51)

The PRIME2 study was conducted at 57 centres which screened at least one participant in 11 countries/regions worldwide (Canada, Chile, France, Hungary, Italy, Portugal, Republic of Korea, Spain, Taiwan, UK and US).(51) Of these, 55 centres randomised at least one participant.(52) One trial site, which enrolled three patients, was located in the UK.(60)

B.2.3.4 Trial drugs and concomitant medications

Patients in the PRIME2 and PRIME studies were randomised 1:1 to receive either dupilumab or matching BSC, with randomisation stratified by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no) and country/territory code.(61, 62) Any medication or vaccine received by patients at the time of enrolment or during the study

was recorded.(61, 62) Low to medium potency TCS/TCIs were permitted as background therapies and high potency or super-potent TCS/TCIs were permitted as rescue therapies throughout the study.(61, 62) The list of trial drugs, non-investigational medicinal products (IMP), permitted concomitant therapies and prohibited concomitant therapies is summarised in Table 6..

Table 6. Trial drugs and concomitant medications in PRIME2 and PRIME(61, 62)

Trial drugs	In the dupilumab group, patients received an initial loading dose of 600 mg of dupilumab SC at Day 1 followed by 300 mg of dupilumab SC once Q2W until Week 24. No dose modifications of dupilumab were permitted during the study. In the BSC group, patients received matching BSC with an identical formulation (without dupilumab), dosing schedule and route of administration to the active treatment.
Non-investigational medicinal products	Background therapies included emollients and low to medium potency TCS/TCIs. The application of moisturisers (emollients) once or twice daily was required for patients in both study groups for at least five days during the week before the start of the intervention period and continuously until the end of the study (Week 36). Patients could also be rescued with high potency or super-potent TCS/TCIs as needed throughout the study.
Permitted concomitant therapies	The concomitant use of non-sedating antihistamine administration was permitted during the study, except for treatment of AD or PN, but dose changes were not permitted both from Week 11 to Week 12 and from Week 23 to Week 24.
Prohibited concomitant therapies	The concomitant use of systemic immunosuppressive/immunomodulating drugs, other monoclonal antibodies, phototherapy, naltrexone or other opioid antagonists, gabapentin, pregabalin and thalidomide was prohibited and would lead to treatment discontinuation if used at any point during the study. The concomitant use of paroxetine, fluvoxamine or other SSRIs, SNRIs and amitriptyline or other tricyclic or tetracyclic antidepressants was prohibited except if the dose had been stable for at least three months prior to screening. The concomitant use of intralesional corticosteroid injections and cryotherapy, sedating antihistamines and non-sedating antihistamine used specifically for the treatment of itch secondary to AD or PN was prohibited during the entire study but would not lead to treatment discontinuation.

AD = atopic dermatitis; BSC = best supportive care; PN = prurigo nodularis; Q2W = every two weeks; SC = subcutaneously; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids

B.2.3.5 Outcomes used in the economic model or specified in the scope, including primary outcome

The primary endpoint in PRIME2 was proportion of patients with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 12.(53) The primary endpoint in PRIME was proportion of patients with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 24.(53) Moreover, the proportion of participants with an IGA PN-S 0 or 1 score at Week 24 was a key secondary endpoint in both studies.(53) WI-NRS and IGA-PN can be used in combination to measure the intensity of itch and nodular lesion status, respectively. Use of these efficacy response criteria in combination is supported by UK clinicians as confirmed during the advisory board conducted by Sanofi in December 2022.(1, 63)

The primary cut-off dates for PRIME2 and PRIME were 30th August 2021 and 12th November 2021, respectively.(54) Data from PRIME2 and PRIME were combined in a pre-specified pooled analysis, which was conducted to increase the sample size of patients treated with dupilumab.(53) Proportion of patients with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 12 and from baseline to Week 24 were considered the primary endpoints in the pooled analysis.(53) Key secondary endpoints and other secondary endpoints are listed in Table 7..(64) Exploratory efficacy endpoints are presented in Appendix M.2. The pooled efficacy analysis was pre-specified.(64)

Table 7. Pooled efficacy analysis endpoints(64)

Primary endpoint	• Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 12 (primary endpoint for PRIME2) • Proportion of participants with improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24 (primary endpoint for PRIME)
Key secondary endpoints	• Proportion of participants with IGA PN-S 0 or 1 score at Week 24 • Proportion of participants with both an improvement (reduction) in WI-NRS by ≥4 from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24
Other secondary endpoints	• Proportion of participants with WI-NRS reduction ≥4 over time until Week 24 • Proportion of participants with WI-NRS reduction ≥4 at Week 2 and at Week 4 • Proportion of participants with IGA PN-S 0 or 1 score at Week 4, Week 8 and Week 12 • Proportion of participants with IGA PN-A 0 or 1 score at Week 4, Week 8, Week 12 and Week 24 • Time to onset of effect on pruritus as measured by proportion of participants with an improvement (reduction) in WI-NRS by ≥4 from baseline during the 24-week treatment period • Change from baseline in WI-NRS at Week 12 and Week 24 • Percent change from baseline in WI-NRS at Week 2, Week 4, Week 12 and Week 24 • Percent change from baseline in WI-NRS over time until Week 24 • Onset of action in change from baseline in WI-NRS (first $p<0.05$ difference from BSC in the daily WI-NRS that remains significant at subsequent measurements) until Week 12 • Change from baseline in IGA PN-S score at Week 4, Week 8, Week 12 and Week 24 • Change from baseline in HRQoL, as measured by DLQI to Week 12 and Week 24 • Proportion of participants with DLQI reduction ≥4 from baseline over time until Week 24

DLQI = dermatology life quality index; HRQoL = health-related quality of life; IGA PN-A = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Activity; IGA PN-S = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Stage; PN = prurigo nodularis; WI-NRS = worst-itch numeric rating scale

B.2.3.6 Summary of methodology

The phase III PRIME2 and PRIME studies had similar study designs but differed in the timing of their primary endpoints and locations; however, no change in routine or crossover between arms was allowed. The methodology of the phase III PRIME2 and PRIME studies is summarised in Table 8.. The pooled analysis investigated all subgroups pre-planned in PRIME2 and PRIME along with duration of PN (≥three years, <three years), age at PN onset (≥30 years, <30 years; ≥ median, < median), disseminated or localised PN lesions (>two

body surface area [BSA], ≤two BSA), phototherapy use (yes, no), history of systemic immunosuppressant use (yes, no), history of systemic antipruritic medications (yes, no) and history of systemic immunosuppressant or antipruritic use (yes, no) as additional pre-specified subgroups.(64)

Table 8. Comparative summary of trial methodology(51, 52, 61, 62, 64)

	NCT04202679 (PRIME2)	NCT04183335 (PRIME)
Location	Global	
Trial design	International, multi-centre, parallel group, double-blind, randomised, placebo-controlled trials to evaluate the efficacy and safety of dupilumab in participants with PN whose disease was inadequately controlled on topical prescription therapies or when those therapies were not advisable	
Eligibility criteria for participants	• 18 to 80 years of age • PN diagnosis by a dermatologist ≥three months before screening • Average WI-NRS score ≥7 in the seven days before Day 1 • Total ≥20 PN lesions on both legs, both arms and/or trunk, at screening and on Day 1 • Failed treatment with a two-week course of medium-to-super potent TCS or when TCS was not medically advisable • Applied of topical emollient once or twice daily for ≥five out of seven consecutive days before Day 1	• 18 to 80 years of age • PN diagnosis by a dermatologist ≥three months before screening • Average WI-NRS score ≥7 in the seven days before Day 1 • Total ≥20 PN lesions on both legs, both arms and/or trunk, at screening and on Day 1 • Failed treatment with a two-week course of medium-to-super potent TCS or when TCS was not medically advisable • Applied of topical emollient once or twice daily for ≥five out of seven consecutive days before Day 1
Settings and locations where the data were collected	57 centres in 11 countries/regions worldwide – 27 centres in Europe (Canada, Chile, France, Hungary, Italy, Portugal, Republic of Korea, Spain, Taiwan, UK and US)	63 centres in eight countries/regions worldwide – one centre in Europe (US, Argentina, Mexico, Mainland China, Japan, Russian Federation, Republic of Korea and France)
Trial drugs	In the dupilumab group (n=78) • Dupilumab 300 mg Q2W SC for 24 weeks after an initial loading dose of 600 mg In the BSC group (n=82) • Matched BSC 0 mg Q2W SC for 24 weeks	In the dupilumab group (n=75) • Dupilumab 300 mg Q2W SC for 24 weeks after an initial loading dose of 600 mg In the BSC group (n=76) • Matched BSC 0 mg Q2W SC for 24 weeks
Permitted and disallowed concomitant medication	Permitted concomitant therapies: • Non-sedating antihistamine administration Prohibited concomitant therapies: • Systemic immunosuppressive/ immunomodulating drugs • Other monoclonal antibodies • Phototherapy, including tanning beds • Naltrexone or other opioid antagonists • Gabapentin, pregabalin and thalidomide • Paroxetine, fluvoxamine or other SSRIs	Permitted concomitant therapies: • Non-sedating antihistamine administration Prohibited concomitant therapies: • Systemic immunosuppressive/ immunomodulating drugs • Other monoclonal antibodies • Phototherapy, including tanning beds • Naltrexone or other opioid antagonists • Gabapentin, pregabalin and thalidomide • Paroxetine, fluvoxamine or other SSRIs

	NCT04202679 (PRIME2)	NCT04183335 (PRIME)
	• SNRIs • Amitriptyline or other tricyclic or tetracyclic antidepressants • Intralesional corticosteroid injections and cryotherapy • Sedating antihistamines • Non-sedating antihistamine used specifically for the treatment of itch secondary to AD or PN	• SNRIs • Amitriptyline or other tricyclic or tetracyclic antidepressants • Intralesional corticosteroid injections and cryotherapy • Sedating antihistamines • Non-sedating antihistamine used specifically for the treatment of itch secondary to AD or PN
Primary outcomes	Proportion of patients with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 12	Proportion of patients with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 24
Other outcomes used in the economic model/specified in the scope	Improvement in DLQI, IGA PN-S and IGA PN-A assessed outcomes	Improvement in DLQI, IGA PN-S and IGA PN-A assessed outcomes
Pre-planned subgroups	• Age group (<65, ≥65 years) • Gender (Male, Female) • Region • Territory • Race (Caucasian/White, Black/of African descent, Asian/Oriental, Others) • Ethnicity (Hispanic or Latino, Not Hispanic or Latino) • Baseline weight (<60, ≥60- <90, ≥90 kg) • Baseline BMI (<25, ≥25- <30, ≥30 kg/m^2) • Participants without a current diagnosis of AD • History of atopy (atopic, non-atopic) • Stable use of TCS/TCI (yes, no) • Antidepressant use (yes, no) at baseline • Baseline IGA PN-S moderate versus severe (3, 4) • Participants who have not been impacted by COVID-19 vs. impacted by COVID-19	• Age group (<65, ≥65 years) • Gender (Male, Female) • Region • Territory • Race (Caucasian/White, Black/of African descent, Asian/Oriental, Others) • Ethnicity (Hispanic or Latino, Not Hispanic or Latino) • Baseline weight (<60, ≥60- <90, ≥90 kg) • Baseline BMI (<25, ≥25- <30, ≥30 kg/m^2) • Participants without a current diagnosis of AD • History of atopy (atopic, non-atopic) • Stable use of TCS/TCI (yes, no) • Antidepressant use (yes, no) at baseline • Baseline IGA PN-S moderate versus severe (3, 4) • Participants who have not been impacted by COVID-19 vs. impacted by COVID-19

AD = atopic dermatitis; BMI = body mass index; BSC = best supportive care; COVID-19 = coronavirus disease 2019; DLQI = Dermatology Life Quality Index; IGA PN-A = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Activity; IGA PN-S = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Stage; PN = prurigo nodularis; Q2W = every two weeks; SC = subcutaneous; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; WI-NRS = worst-itch numeric rating scale; UK = United Kingdom; US = United States

B.2.3.7 Baseline patient and disease characteristics

A total of 311 patients were randomised in PRIME2 and PRIME (dupilumab: 153; BSC: 158), comprising the intent-to-treat (ITT) population.(51, 52) Overall, 265 patients completed the 24-week treatment period.(51, 52) One patient in the dupilumab group (PRIME2) and one

patient in the BSC group (PRIME) were randomised but did not enter the study intervention period.(53)

Patient baseline characteristics and disease characteristics were generally balanced between treatment groups (Table 9.).(53) The mean patient age was 49.5 years (range: 18, 80) and 65.3% were female and the mean duration of PN was 5.56 years.(53) [redacted] of enrolled patients were from the European Union (France, Italy, Hungary, Portugal, Spain and UK), [redacted] were from North America (US and Canada) and [redacted] were from Rest of World (Russia, Japan, China, Taiwan, South Korea, Argentina, Chile and Mexico).(53) UK dermatology experts who participated in an advisory board conducted by Sanofi in April 2022 confirmed the patients enrolled in PRIME2 and PRIME are a fair representation of PN patients in UK clinical practice.(63)

Overall, 43.4% of patients had a history of atopy, [redacted] has history of asthma, 66.3% had an IGA PN-S score of 3 ('moderate'), 33.7% had an IGA-PN-S score of 4 ('severe'), [redacted] had an Investigator's Global Assessment for Prurigo Nodularis – Activity (IGA PN-A) score of 3 ('moderate') and [redacted] had an IGA PN-A score of 4 ('severe').(53) Over half of patients were on a stable regimen of TCS/TCI.(53) [redacted] of patients in the pooled analysis had at least borderline anxiety (defined as HADS – anxiety subscale [HADS-A] score of ≥8) and [redacted] had at least borderline depression (defined as HADS – depression subscale [HADS-D] score of ≥8, respectively).(53)

Table 9. Characteristics of participants in the studies across treatment groups (ITT population; PRIME2, PRIME and pooled analysis)(51-53)

Characteristic	PRIME2		PRIME		Pooled ITT analysis	
	BSC (n=82)	Dupilumab (n=78)	BSC (n=76)	Dupilumab (n=75)	BSC (N=158)	Dupilumab 300 mg Q2W (N=153)
Age, years, mean (SD)	46.7 (15.2)	51.0 (15.8)	51.1 (15.8)	49.2 (17.4)	48.8 (15.6)	50.1 (16.6)
Male (%)	31 (37.8)	26 (33.3)	28 (36.8)	23 (30.7)	59 (37.3)	49 (32.0)
Territory[a]						
North America	14 (17.1)	12 (15.4)	18 (23.7)	17 (22.7)	[redacted]	[redacted]
European Union	37 (45.1)	40 (51.3)	2 (2.6)	1 (1.3)	[redacted]	[redacted]
Rest of World	31 (37.8)	26 (33.3)	56 (73.7)	57 (76.0)	[redacted]	[redacted]
Race, n (%)						
White	48 (58.5)	48 (61.5)	45 (59.2)	35 (46.7)	93 (58.9)	83 (54.2)
Black	5 (6.1)	3 (3.8)	3 (3.9)	8 (10.7)	8 (5.1)	11 (7.2)
Asian	27 (32.9)	25 (32.1)	25 (32.9)	29 (38.7)	52 (32.9)	54 (35.3)
Hispanic or Latino ethnicity, n (%)	11 (13.4)	10 (12.8)	21 (27.6)	18 (24.0)	32 (20.3)	28 (18.3)

Characteristic	PRIME2		PRIME		Pooled ITT analysis	
	BSC (n=82)	Dupilumab (n=78)	BSC (n=76)	Dupilumab (n=75)	BSC (N=158)	Dupilumab 300 mg Q2W (N=153)
Weight, kg, mean (SD)	75.04 (19.73)	73.86 (17.50)	71.37 (16.97)	75.22 (17.26)	73.29 (18.50)	74.53 (17.34)
BMI, kg/m^2, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PN, years, mean (SD)[b]	5.48 (6.97)	5.36 (6.90)	5.40 (6.21)	6.01 (7.55)	5.44 (6.60)	5.68 (7.21)
History of atopy, n (%)[c]	40 (48.8)	34 (43.6)	28 (36.8)	33 (44.0)	68 (43.0)	67 (43.8)
History of asthma, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stable use of TCS/TCI, n (%)[d]	46 (56.1)	44 (56.4)	45 (59.2)	47 (62.7)	91 (57.6)	91 (59.5)
WI-NRS score, mean (SD)	8.5 (1.0)	8.5 (1.0)	8.3 (1.1)	8.6 (0.9)	8.4 (1.1)	8.6 (0.9)
IGA PN-S score, mean (SD)	3.4 (0.5)	3.4 (0.5)	3.3 (0.5)	3.3 (0.5)	[redacted]	[redacted]
IGA PN-S categorical score, n (%)						
3 (moderate)	49 (60.5)	49 (62.8)	53 (70.7)	54 (72.0)	102 (65.4)	103 (67.3)
4 (severe)	32 (39.5)	29 (37.2)	22 (29.3)	21 (28.0)	54 (34.6)	50 (32.7)
IGA PN-A score, mean (SD)	3.4 (0.6)	3.4 (0.6)	3.3 (0.6)	3.3 (0.6)	[redacted]	[redacted]
IGA PN-A categorical score, n (%)						
3 (moderate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 (severe)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin pain – NRS score, mean (SD)	7.1 (2.5)	7.3 (2.4)	7.2 (2.3)	7.2 (2.5)	7.2 (2.4)	7.2 (2.5)
Sleep – NRS score, mean (SD)	4.2 (2.5)	4.4 (2.3)	4.3 (2.2)	4.4 (2.4)	4.2 (2.4)	4.4 (2.4)
Number of lesions from PAS, n (%)						
20-100	52 (63.4)	47 (60.3)	52 (69.3)	54 (72.0)	[redacted]	[redacted]
>100	30 (36.6)	31 (39.7)	23 (30.7)	21 (28.0)	[redacted]	[redacted]
Exact number of lesions in representative area from PAS, mean (SD)	26.4 (18.8)	25.6 (18.7)	25.1 (16.7)	27.0 (26.7)	[redacted]	[redacted]
Healed lesions from PAS, n (%)						
0-24%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25-49%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-74%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75-99%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HADS total score, mean (SD)	15.9 (8.4)	16.2 (7.7)	14.3 (8.0)	14.5 (8.2)	[redacted]	[redacted]
HADS-A score ≥8, n (%)	46 (56.8)	50 (64.1)	45 (60.0)	41 (54.7)	[redacted]	[redacted]
HADS-D score ≥8, n (%)	31 (38.3)	30 (38.5)	28 (37.3)	26 (34.7)	[redacted]	[redacted]
DLQI score, mean (SD)	18.2 (7.0)	18.2 (6.5)	15.7 (7.3)	17.8 (7.1)	17.0 (7.2)	18.0 (6.7)

Characteristic	PRIME2		PRIME		Pooled ITT analysis	
	BSC (n=82)	Dupilumab (n=78)	BSC (n=76)	Dupilumab (n=75)	BSC (N=158)	Dupilumab 300 mg Q2W (N=153)
Antidepressant use at baseline, n (%)	8 (9.8)	7 (9.0)	9 (11.8)	9 (12.0)	[redacted]	[redacted]

AD = atopic dermatitis; BMI = body mass index; BSC = best supportive care; DLQI = dermatology life quality index; HADS = hospital anxiety and depression scale; HADS-A = hospital anxiety and depression scale – anxiety subscale; HADS-D = hospital anxiety and depression scale – depression subscale; IGA PN-A = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Activity; IGA PN-S = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Stage; ITT = intent-to-treat; NRS = numeric rating scale; PAS = prurigo activity score; PN = prurigo nodularis; SD = standard deviation; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; Q2W = every two weeks; UK = United Kingdom; USA = United States of America; WI-NRS = worst-itch numeric rating scale

[a] North America = USA and Canada; European Union = France, Italy, Hungary, Portugal, Spain and UK; Rest of World = Russia, Japan, China, Taiwan, South Korea, Argentina, Chile and Mexico

[b] Derived as (Year of randomisation - Year of first diagnosis of PN) + (month of randomisation - month of first diagnosis of PN)/12

[c] Defined as having a medical history of AD, allergic rhinitis/rhinoconjunctivitis, asthma, food allergy or eosinophilic esophagitis

[d] Stable regimen for TCS is defined as maintaining the same medicine (low to medium potency TCS) and maintaining the same frequency of treatment (once or twice daily) used from two weeks prior to screening. Stable regimen for TCI is defined as maintaining the same medicine and treatment frequency (once or twice daily) used from two weeks prior to screening

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Study population

In the PRIME2 study, 160 patients were randomised 1:1 to the two treatment groups (dupilumab: 78; BSC: 82[4]).(52) All 160 randomised patients were included in the ITT population (used for all primary and secondary efficacy endpoints) and 159 randomised patients (dupilumab: 77; BSC: 82) were included in the safety population (defined as all patients randomly assigned to study intervention who received at least one dose of study drug).(52)

In the PRIME study, 151 patients were randomised 1:1 to the two treatment groups (dupilumab: 75; BSC: 76).(51) All 151 randomised patients were included in the ITT population (used for all primary and secondary efficacy endpoints) and 150 randomised[5] patients (dupilumab: 75; BSC: 75) were included in the safety population (defined as all patients randomly assigned to study intervention who received at least one dose of study drug).(51)

The pooled analysis included efficacy data from PRIME2 and PRIME across the 24-week treatment period.(64) Overall, 311 patients in ITT populations in PRIME2 and PRIME were included in the pooled ITT population for all efficacy endpoints (dupilumab: 153; BSC: 158), as depicted in the CONSORT diagram in Appendix D.2.(51-53) The pooled analysis of safety outcomes included data from the safety population, defined as all patients who received at least one dose of study intervention and analysed according to the intervention actually received (dupilumab: 152; BSC: 157).(51, 52, 54)

B.2.4.2 Statistical analyses

Statistical analyses undertaken in pooled efficacy analysis and the individual PRIME2 and PRIME studies are summarised in Table 10.(65, 66)

[4] Differences in the number of patients in each treatment group can be explained by patients deciding not to take part in the study after randomisation or patients becoming ineligible for the study due to not following protocol deviations after randomisation. Moreover, stratification and block randomisation were used to assign patients to treatment groups; however, it is expected that some blocks may not be filled completely, resulting in a slight imbalance in patient numbers.

[5] One randomised patient in the PRIME study decided against receiving the study drug out of fear of exposure to COVID-19.

Table 10. Summary of statistical analyses(61, 62, 65, 66)

Trial	Pooled efficacy analysis	NCT04202679 (PRIME2) and NCT04183335 (PRIME)[a]
Hypothesis objective	See NCT04202679 (PRIME2) and NCT04183335 (PRIME) column	Null hypothesis: No treatment difference between dupilumab and BSC. Alternative hypothesis: There is a treatment difference between dupilumab and BSC.
Statistical analysis	For the primary endpoint and binary secondary endpoints assessments, the Cochran–Mantel–Haenszel test was used, adjusted for randomisation strata (documented history of atopy, stable use of TCS/TCI and region) and baseline antidepressant use. Non-responders were considered patients receiving prohibited medications/procedures (including immunosuppressants), rescue treatment or with missing values. Time to first WI-NRS improvement was analysed using a Cox proportional hazards model, which included treatment, stratification factors and baseline antidepressant use. Continuous secondary endpoints were analysed using an analysis of covariance model; efficacy data after rescue treatment were set to missing and imputed by worst-observation carried forward. Missing data after treatment discontinuation for lack of efficacy were imputed by WOCF and other missing data were imputed by multiple imputation.	The primary analyses of the primary endpoint, key secondary efficacy endpoints and other secondary efficacy endpoints that measure binary responses were conducted by using Cochran–Mantel–Haenszel test adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no). Patients who discontinued treatment before Week 12/Week 24 and had their off-study treatment values measured up to Week 12/Week 24 were included in the analysis. Patients who received prohibited medications/procedures (including immunosuppressants) and/or rescue medications prior to Week 12/Week 24 or who had missing data at Week 12/Week 24 were considered non-responders. Continuous secondary efficacy endpoints were analysed using an analysis of covariance model with intervention group, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region (countries combined), baseline antidepressant use (yes or no) and relevant baseline measurement as covariates. Patients who received prohibited medications/procedures (including immunosuppressants) and/or rescue medications prior to Week 12/Week 24 or who had missing data at Week 12/Week 24 were censored. The comparison between dupilumab and BSC was tested based on a hierarchical order to control for type I error at a two-sided alpha level of 0.05. In the as-observed supplementary analyses, all observations were used for analysis regardless of use of rescue therapy.
Sample size, power calculation	See NCT04202679 (PRIME2) and NCT04183335 (PRIME) column	The study was powered to evaluate the effect of dupilumab on WI-NRS reduction of ≥4 from baseline to Week 12/Week 24, with the response rate assumed to be 11% and 39% in the BSC and dupilumab groups, respectively. Assuming a dropout rate of 15% during 12 weeks of treatment, approximately 150 patients (75 per treatment group) were required to detect a difference of 28% between treatment groups with 90% power at a Fisher exact test at two-sided significance level of 0.05.
Data management, patient withdrawals	See NCT04202679 (PRIME2) and NCT04183335 (PRIME) column	Patients could withdraw from the study at any time at their own request or be withdrawn by the investigator for safety, behavioural, compliance or administrative reasons. Patients who were lost to follow-up were also considered to have withdrawn from the study. All study withdrawals were recorded in the electronic case report form. Discontinuation of study treatment did not result in automatic withdrawal from the study; patients

Trial	Pooled efficacy analysis	NCT04202679 (PRIME2) and NCT04183335 (PRIME)[a]
		who discontinued treatment were continued to be evaluated for both efficacy and safety.
	See NCT04202679 (PRIME2) and NCT04183335 (PRIME) column	For 'proportion' endpoints, off-study treatment data was included in the analysis for patients who discontinued study treatment before the end of the treatment period. Patients with missing data were considered non-responders. For 'time-to-event' endpoints, off-study treatment data was included in the analysis for patients who discontinued study treatment before the end of the treatment period. Analyses were censored for patients with missing data. For 'continuous' endpoints, all data collected following schedule after treatment discontinuation was included in the analysis for patients who discontinued study treatment before the end of the treatment period. The WOCF approach was used to impute missing data for patients who discontinued study treatment due to lack of efficacy. The MI approach was used to impute missing data for patients who discontinued study treatment for reasons other than lack of efficacy.

BSC = best supportive care; MI = multiple imputation; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; WI-NRS = worst-itch numeric rating scale; WOCF = worst-observation carried forward
[a] The same statistical analyses were conducted for PRIME2 and PRIME.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The quality assessment of PRIME2 and PRIME, which are high-quality studies (double-blinded RCTs with generally balanced patient demographics and characteristics) and are pertinent to the decision problem, are provided in Table 11. below. A detailed quality assessment of PRIME2 and PRIME is provided in Appendix D.3.

Table 11. Quality assessment results for PRIME2 and PRIME(51, 52, 61, 62)

Trial number (acronym)	NCT04202679 (PRIME2)	NCT04183335 (PRIME)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in dropouts between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

ITT = intent-to-treat

B.2.6 Clinical effectiveness results of the relevant studies

Outcomes for the individual PRIME2 and PRIME studies and the pooled analysis are summarised in Table 12.. Both PRIME2 and PRIME met their individual primary and key secondary endpoints.(51, 52) When results from PRIME2 and PRIME were pooled to increase the sample size, dupilumab continued to demonstrate statistically significant benefit over BSC across all primary and key secondary endpoints.(53)

Table 12. Summary of clinical effectiveness (ITT population; PRIME2, PRIME and pooled analysis)(51, 52, 64, 67)

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)	
Patients with IGA PN-S 0 or 1 at Week 24						
Responders, n (%)	13 (15.9)	35 (44.9)	14 (18.4)	36 (48.0)	27 (17.1)	71 (46.4)
Nominal p value vs. BSC[a]	<0.0001		0.0004		<0.0001	
OR, 95% CI vs. BSC[b]	4.4 (2.02, 9.55)		4.0 (1.81, 8.98)		4.2 (2.42, 7.37)	
RRD (%), 95% CI vs. BSC[b]	30.8 (16.37, 45.22)		28.3 (13.41, 43.16)		29.6 (19.22, 39.94)	
Patients with both an improvement (reduction) in WI-NRS by ≥4 points and IGA PN-S score of 0 or 1 at Week 24						
Responders, n (%)	7 (8.5)	25 (32.1)	7 (9.2)	29 (38.7)	14 (8.9)	54 (35.3)
Nominal p value vs. BSC[a]	0.0001		<0.0001		<0.0001	
OR, 95% CI vs. BSC[b]	6.1 (2.03, 18.11)		6.9 (2.49, 19.05)		6.5 (3.05, 13.67)	
RRD (%), 95% CI vs. BSC[b]	25.5 (13.09, 37.86)		29.6 (16.42, 42.81)		27.5 (18.43, 36.51)	
Patients with IGA PN-S 0 or 1 at Week 12[c]						
Responders, n (%)	10 (12.2)	20 (25.6)	9 (11.8)	24 (32)	19 (12.0)	44 (28.8)
Nominal p value[a]	0.0194		0.0027		0.0002	
Change in IGA PN-S score from baseline to Week 4[c]						
LS mean (SE)	[redacted]		[redacted]		[redacted]	
Nominal p value vs. BSC	[redacted]		[redacted]		[redacted]	

Endpoint	PRIME2		PRIME		Pooled ITT analysis	
	BSC (n=82)	Dupilumab (n=78)	BSC (n=76)	Dupilumab (n=75)	BSC (N=158)	Dupilumab (N=153)
Difference (95% CI) dupilumab vs. BSC	[redacted]		[redacted]		[redacted]	
Change in IGA PN-S score from baseline to Week 12[c]						
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nominal p value vs. BSC	[redacted]		[redacted]		[redacted]	
Difference (95% CI) dupilumab vs. BSC	[redacted]		[redacted]		[redacted]	
Change in IGA PN-S score from baseline to Week 24[c]						
LS mean (SE)	-1.07 (0.20)	-2.03 (0.20)	-0.62 (0.17)	-1.59 (0.17)	[redacted]	[redacted]
Nominal p value vs. BSC	<0.0001		<0.0001		[redacted]	
Difference (95% CI) dupilumab vs. BSC	-0.97 (-1.30, -0.63)		-0.97 (-1.32, -0.62)		[redacted]	
Patients with IGA PN-A score of 0 or 1 at Week 8[a]						
n (%)	13 (15.9)	18 (23.1)	3 (3.9)	17 (22.7)	[redacted]	[redacted]
Nominal p value	NR		0.0038		[redacted]	
Patients with IGA PN-A score of 0 or 1 at Week 12[a]						
n (%)	16 (19.5)	33 (42.3)	11 (14.5)	26 (34.7)	[redacted]	[redacted]
Nominal p value	0.0004		0.025		[redacted]	
Patients with IGA PN-A score of 0 or 1 at Week 24[a]						
n (%)	15 (18.3)	40 (51.3)	15 (19.7)	45 (60.0)	[redacted]	[redacted]
Nominal p value	<0.0001		<0.0001		[redacted]	
Change in Skin Pain-NRS from baseline to Week 24[c]						
LS mean (SE)	-2.74 (0.51)	-4.35 (0.53)	-2.16 (0.44)	-4.33 (0.43)	[redacted]	[redacted]
Nominal p value vs. BSC	0.0003		<0.0001		[redacted]	
Difference (95% CI) dupilumab vs. BSC	-1.61 (-2.49, -0.73)		-2.17 (-3.07, -1.28)		[redacted]	
Change in Sleep-NRS from baseline to Week 24[c]						
LS mean (SE)	0.76 (0.45)	1.30 (0.46)	1.27 (0.34)	2.71 (0.33)	[redacted]	[redacted]
Nominal p value vs. BSC	0.1658		<0.0001[d]		[redacted]	
Difference (95% CI) dupilumab vs. BSC	0.54 (-0.22, 1.30)		1.44 (0.75, 2.13)		[redacted]	
Percentage change in WI-NRS from baseline to Week 24[c]						
LS mean (SE)	-36.18 (6.21)	-59.34 (6.39)	-22.22 (5.74)	-48.89 (5.61)	-27.97 (4.23)	-53.44 (4.27)
Nominal p value vs. BSC	<0.0001		<0.0001		<0.0001	
Difference (95% CI)	-23.16 (-33.81, -12.51)		-26.67 (-38.44, -14.90)		-25.47 (-33.45, -17.48)	
Change in WI-NRS from baseline to Week 12[c]						
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nominal p value vs. BSC	[redacted]		[redacted]		[redacted]	

Endpoint	PRIME2		PRIME		Pooled ITT analysis	
	BSC (n=82)	Dupilumab (n=78)	BSC (n=76)	Dupilumab (n=75)	BSC (N=158)	Dupilumab (N=153)
Difference (95% CI) dupilumab vs. BSC	[redacted]		[redacted]		[redacted]	
Percentage change in WI-NRS from baseline to Week 12[c]						
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nominal p value vs. BSC	[redacted]		[redacted]		[redacted]	
Difference (95% CI) dupilumab vs. BSC	[redacted]		[redacted]		[redacted]	
Change in DLQI from baseline to Week 24[c]						
LS mean (SE)	-6.77 (1.18)	-13.16 (1.21)	-5.77 (1.05)	-11.97 (1.02)	-6.27 (0.77)	-12.56 (0.77)
Nominal p value vs. BSC	<0.0001		<0.0001		<0.0001	
Difference (95% CI) dupilumab vs. BSC	-6.39 (-8.42, -4.36)		-6.19 (-8.34, -4.05)		-6.29 (-7.75, -4.83)	
Change in DLQI from baseline to Week 12[c]						
LS mean (SE)	-7.05 (1.12)	-12.07 (1.16)	-5.67 (0.90)	-10.95 (0.89)	[redacted]	[redacted]
Nominal p value vs. BSC	<0.0001		<0.0001		[redacted]	
Difference (95% CI) dupilumab vs. BSC	-5.02 (-6.96, -3.09)		-5.27 (-7.13, -3.41)		[redacted]	
Change in HADS total score from baseline to Week 24[c]						
LS mean (SE)	-2.59 (1.03)	-5.55 (1.06)	-2.02 (0.94)	-4.62 (0.93)	[redacted]	[redacted]
Nominal p value vs. BSC	0.0010		0.0082		[redacted]	
Difference (95% CI) dupilumab vs. BSC	-2.96 (-4.73, -1.19)		-2.60 (-4.52, -0.67)		[redacted]	
Change in HADS-A subscale score from baseline to Week 24[c]						
LS mean (SE)	-1.96 (0.63)	-3.34 (0.65)	-1.15 (0.56)	-2.67 (0.55)	[redacted]	[redacted]
Nominal p value vs. BSC	0.0122		0.0084		[redacted]	
Difference (95% CI) dupilumab vs. BSC	-1.38 (-2.46, -0.30)		-1.52 (-2.66, -0.39)		[redacted]	
Change in HADS-D subscale score from baseline to Week 24[c]						
LS mean (SE)	-0.58 (0.52)	-2.14 (0.54)	-0.86 (0.48)	-1.92 (0.47)	[redacted]	[redacted]
Nominal p value vs. BSC	0.0008		0.0335		[redacted]	
Difference (95% CI) dupilumab vs. BSC	-1.56 (-2.46, -0.65)		-1.06 (-2.03, -0.08)		[redacted]	

BSC = best supportive care; CI = confidence interval; DLQI = dermatology life quality index; HADS = hospital anxiety and depression scale; HADS-A = hospital anxiety and depression scale – anxiety subscale; HADS-D = hospital anxiety and depression scale – depression subscale; IGA PN-A = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Activity; IGA PN-S = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Stage; ITT = intent-to-treat; LS = least squares; NRS = numeric rating scale; OR = odds ratio; Q2W = every two weeks; RRD = response ratio; SE = standard error; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; WI-NRS = worst-itch numeric rating scale

[a] Cochran-Mantel Haenszel test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region

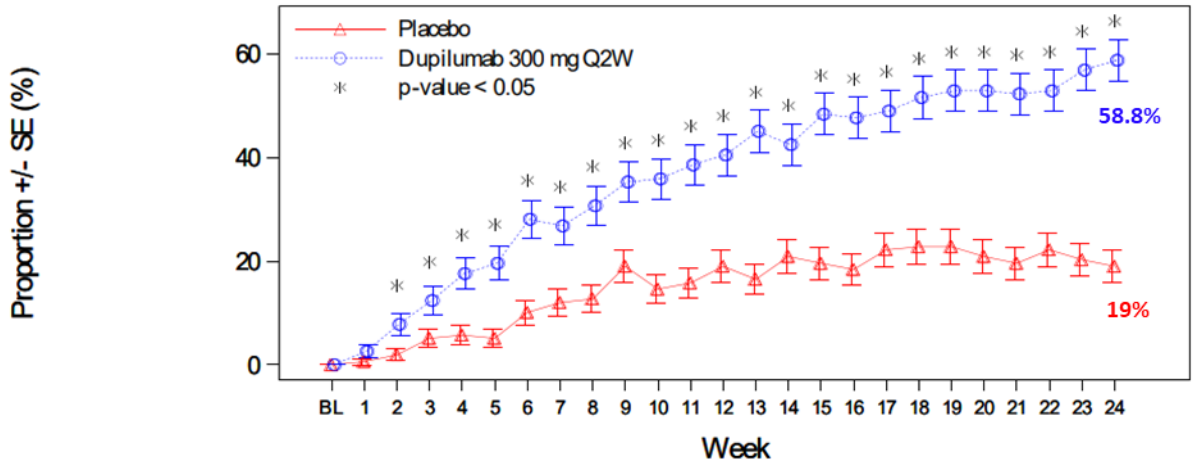
and baseline anti-depressant use (yes or no). In addition, the pooled analysis was also adjusted by study indicator (PRIME2 or PRIME)
[b] Derived from the Mantel-Haenszel estimator
[c] Each of the imputed complete data were analysed by fitting an ANCOVA model with the corresponding baseline value, intervention group, documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region, baseline anti-depressant use (yes or no) and study indicator (PRIME2 or PRIME) as covariates
[d] Nominal p-value for PRIME as not part of the hierarchical testing procedure

B.2.6.1 Primary and key secondary efficacy endpoints: reduction in itch

Dupilumab treatment resulted in continuous, clinically meaningful and statistically significant improvement in PN symptoms compared with the BSC group, as measured by the primary and key secondary efficacy endpoints in both the pooled ITT analysis and the individual studies.

The proportion of patients in the pooled ITT analysis with WI-NRS improvement by ≥4 points was significantly greater in the dupilumab group compared to the BSC group.(53) Mean WI-NRS score was comparable at baseline (8.4 in the BSC group vs. 8.6 in the dupilumab group).(53) At Week 2, the proportion of patients with WI-NRS improvement was already significantly greater in the dupilumab group than in the BSC group; this difference was maintained up to Week 24 (Figure 7).(53) At Week 12, the proportion of patients with WI-NRS improvement was 40.5% in the dupilumab group vs. 19% in the BSC group (nominal p<0.0001); at Week 24, the proportions of patients in the dupilumab group further increased to 58.8% while in the BSC group remained the same (19%; nominal p<0.0001).(53) The individual PRIME2 and PRIME studies also demonstrated the statistically significant benefit of dupilumab over BSC.(51, 52)

Figure 7. Proportion of patients with an improvement in WI-NRS (≥4 points) from baseline to Week 24 (ITT population; PRIME2, PRIME and pooled analysis)(53)



BL = baseline; ITT = intent-to-treat; Q2W = every two weeks; SE = standard error; WI-NRS = worst-itch numeric rating scale
Note: Values for response at Week 24 are shown inside the graph.

In addition, the proportion of patients with concurrent reduction in both WI-NRS and skin lesions was statistically significant in the pooled dupilumab group compared to the pooled BSC group (35.3% vs. 8.9%; nominal p<0.0001), with the benefit of dupilumab over BSC being supported by the individual study results.(51-53)

B.2.6.2 Other secondary efficacy endpoints: reduction in itch

In the pooled ITT analysis, the LS mean percentage change in WI-NRS was significantly greater in the dupilumab group compared to the BSC group both from baseline to Week 12 [redacted] and from baseline to Week 24 (53.44% vs. 27.97%; nominal p<0.0001).(53) The individual PRIME2 and PRIME studies also demonstrated statistically significant benefit of dupilumab over BSC.(51, 52)

B.2.6.3 Other secondary efficacy endpoints: treatment effect on skin lesions

Results from the individual studies as well as the pooled ITT analysis demonstrated that dupilumab treatment resulted in significant reduction of skin lesions. The mean IGA PN-S score in the pooled ITT analysis and individual studies gradually decreased (improved) over time with significant difference in IGA PN-S score change reported in the dupilumab group compared to the BSC group.(51-53) In the pooled ITT analysis, the greatest treatment difference was reported at Week 24 (LS mean difference dupilumab vs. BSC: [redacted], consistent with the statistically significant benefit of dupilumab over BSC observed in the individual studies.(51-53)

The proportion of patients in the pooled ITT analysis with IGA PN-S 0 or 1 score was significantly greater in the dupilumab group compared to the BSC group from Week 8 and remained significant during the 24-week treatment period.(53) The proportion of patients in the pooled ITT analysis with IGA PN-S 0 or 1 score was 28.8% in the dupilumab group compared to 12% in the BSC group at Week 12 (nominal p=0.0002).(53) The greatest treatment difference was reported at Week 24 with 46.4% of patients in the dupilumab group achieving IGA PN-S 0 or 1 score compared to 17.1% of patients in the BSC group (nominal p<0.0001; Figure 8).(53, 67) The individual PRIME2 and PRIME studies also demonstrated a consistent and statistically significant benefit of dupilumab over BSC.(51, 52)

Figure 8. Proportion of patients with IGA PN-S 0 to 1 score from baseline to Week 24 (ITT population; PRIME2, PRIME and pooled analysis)(53)

BL = baseline; IGA PN-S = Investigator's Global Assessment 0 or 1 score for PN – Stage; ITT = intent-to-treat; Q2W = every two weeks
Note: Values for response at Week 24 are shown inside the graph.

B.2.6.4 Other secondary efficacy endpoints: treatment effect on measures of prurigo activity

The proportion of patients in the pooled ITT analysis with IGA PN-A score of 0 or 1[6] was significantly greater in the dupilumab group compared to the BSC group as early as Week 4 (12.4% vs. 4.4%, nominal p=0.0293) and remained nominally significant during the 24-week treatment period.(67) The greatest treatment difference was reported at Week 24 with [redacted] of patients in the dupilumab group achieving IGA PN-A score of 0 or 1 compared to [redacted] of patients in the BSC group ([redacted]; Figure 9).(53, 67)

The individual PRIME2 and PRIME studies also demonstrated the statistically significant benefit of dupilumab over BSC. The effect of treatment increased the proportion of patients with IGA PN-A score of 0 or 1 compared to BSC, starting at Week 12 for PRIME2 (nominal p=0.0004) and at Week 8 for PRIME (nominal p=0.0038) and was maintained throughout the treatment period.(51-53)

[6] N.B., as shown in Table 9 – patients were enrolled with IGA PN-A scores of 3 or 4

Figure 9. Proportion of patients with IGA PN-A score of 0 to 1 from baseline to Week 24 (ITT population; PRIME2, PRIME and pooled analysis)(53)

BL = baseline; IGA PN-A = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Activity; ITT = intent-to-treat; Q2W = every two weeks
Note: Values for response at Week 24 are shown inside the graph.

B.2.6.5 Other secondary efficacy endpoints: patient-reported outcomes

Treatment with dupilumab significantly increased patient HRQoL, reported as a DLQI decrease from baseline to Week 12 and Week 24, in both the individual PRIME2 and PRIME studies and in the pooled ITT analysis compared to BSC.(51-53, 67)

In the pooled ITT analysis, the dupilumab treatment effect on DLQI decrease from baseline was nominally significant as early as Week 4 (nominal p<0.0001) and increased throughout the treatment period (Figure 10).(53) The LS mean difference in change from baseline versus BSC, was [redacted] at Week 12 and -6.29 (95% CI: -7.75, -4.83; nominal p<0.0001) at Week 24, surpassing the clinically meaningful between-group threshold of 4.0.(53, 67) In a post-hoc analysis of the pooled ITT population, the proportion of participants with a ≥9-point decrease in DLQI from baseline to Week 24 was 64.7% in the dupilumab group compared to 22.8% in the BSC group (nominal p<0.0001).(53)

Figure 10. DLQI LS mean change from baseline up to Week 24 (ITT population; PRIME2, PRIME and pooled analysis)(53)

BL = baseline; DLQI = dermatology life quality index; ITT = intent-to-treat; LS = least squares; Q2W = every two weeks; SE = standard error
Note: Values for response at Week 24 are shown inside the graph.

In the pooled ITT analysis, treatment with dupilumab resulted in a nominally significant improvement in total HADS score from baseline to Week 24 compared to BSC (LS mean difference: [redacted].(53) The statistically significant benefit of dupilumab over BSC was also demonstrated in PRIME2 with nominally significant differences (nominal p=0.0010) and in PRIME with statistically significant differences (nominal p=0.0082).(51-53) Treatment with dupilumab also resulted in significantly greater improvements in the HADS-A and HADS-D) compared to BSC in both the individual PRIME2 and PRIME studies and in the pooled ITT analysis (nominal [redacted] for all).(53)

B.2.6.6 Exploratory efficacy endpoints: skin pain and impaired sleep quality associated with PN

In the pooled ITT analysis, treatment with dupilumab over time resulted in a greater decrease in the weekly average Skin Pain-NRS score compared to the BSC group.(53) The LS mean difference from baseline in average Skin Pain-NRS score was greater in the dupilumab group compared to the BSC group as early as Week 2 (-0.42; 95% CI: -0.80, -0.05; nominal p=0.0259). This difference gradually increased for the remaining treatment period with the greatest difference observed at Week 24 (LS mean difference in change from baseline dupilumab vs. BSC: [redacted]; nominal [redacted]; Figure 11).(51-

53) The individual PRIME2 and PRIME studies also demonstrated the statistically significant benefit of dupilumab over BSC.

Figure 11. Skin Pain-NRS LS mean change from baseline up to Week 24 (ITT population; PRIME2, PRIME and pooled analysis)(53)

BL = baseline; ITT = intent-to-treat; NRS = numeric rating scale; LS = least squares; Q2W = every two weeks; SE = standard error
Note: Values for response at Week 24 are shown inside the graph.

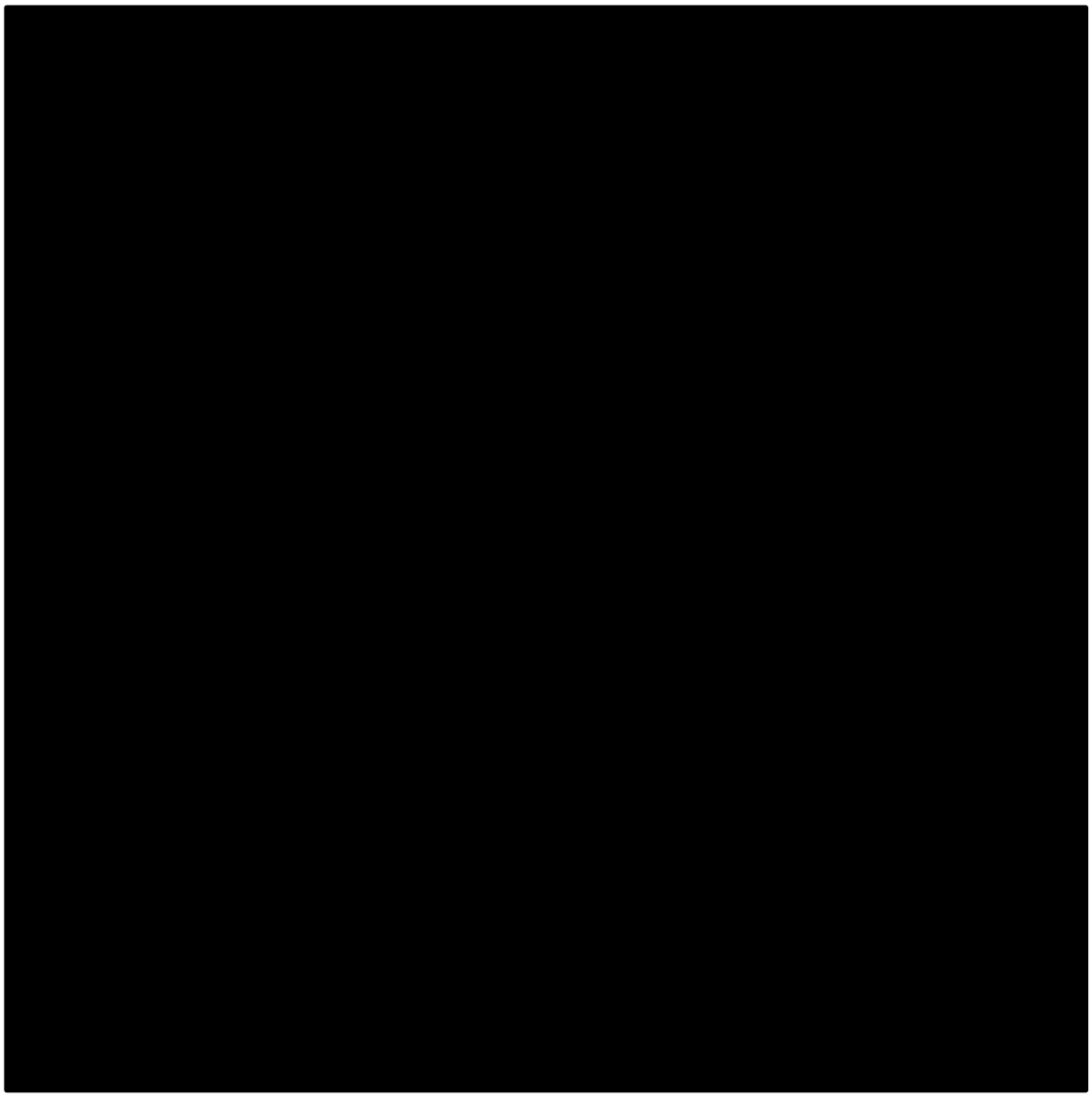
In the pooled ITT analysis, a nominally significant improvement in weekly average Sleep-NRS score from baseline to Week 24 was reported in the dupilumab group compared to the BSC group (LS mean difference in change from baseline vs. BSC: [redacted].(53) PRIME also reported statistically significant benefit of dupilumab over BSC, whereas in PRIME2, although trending towards improvement, the difference reported was not statistically significant.(51, 52)

B.2.7 Subgroup analysis

The proportion of patients with WI-NRS improvement by ≥4 points from baseline to Week 24 was consistent across most pre-specified subgroups (Figure 12).(53) Notably, dupilumab demonstrated significant benefit over BSC in patients with and without history of atopy and regardless of prior systemic immunosuppressant and/or antipruritic medication use.(53) Odds ratios (OR) and 95% CI could not be estimated for several subgroups (age: ≥65 to >75 years, age: ≥75 years, race: Black/African descent, race: other, body weight: <60 kg and phototherapy use: yes), but response rates trended in favour of dupilumab over BSC.(53) Only three patients were included in the disseminated or localised PN lesions: ≤two BSA

subgroup, which was insufficient to make any conclusions about the relative efficacy of dupilumab vs. BSC (discussed further in the context of PN as a rare disease in Section B.2.12).(53)

Figure 12. Forest plot of proportion of patients with WI-NRS improvement by ≥4 points from baseline to Week 24 by pre-specified subgroups (ITT population; pooled analysis)(53)

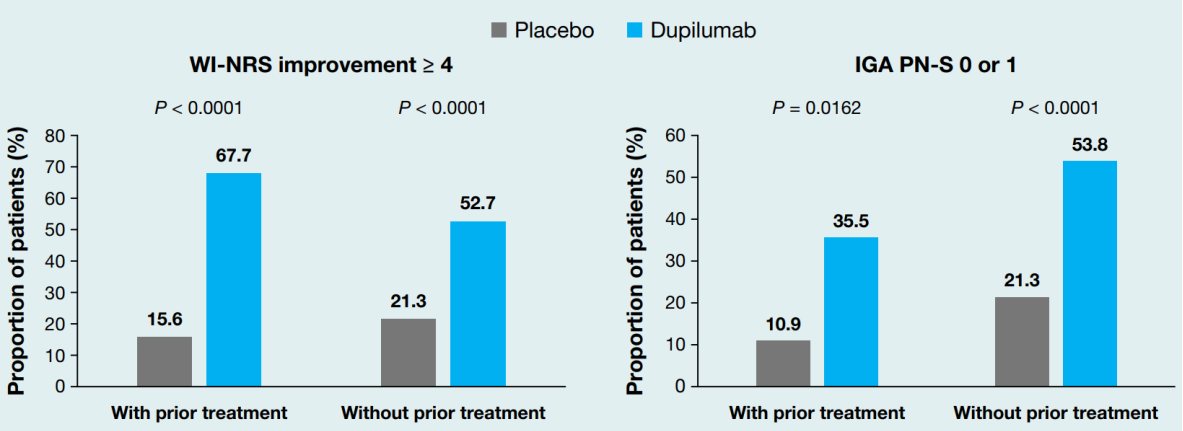


AD = atopic dermatitis; BMI = body mass index; BSA = body surface area; IGA PN-S = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Stage; ITT = intent-to-treat; PN = prurigo nodularis; OR = odds ratio; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; WI-NRS = worst-itch numeric rating scale

A post-hoc analysis was also conducted to investigate the efficacy of dupilumab in patients with PN who received prior treatment with immunosuppressants or phototherapy.(68) The proportion of patients with WI-NRS improvement by ≥4 points was significantly greater in the dupilumab group compared to the BSC group regardless of prior treatment with immunosuppressants or phototherapy (Figure 13).(68) Similarly, more patients achieved

clear or almost clear skin (IGA PN-S 0 or 1) in the dupilumab group than in the BSC group irrespective of prior treatment.(68)

Figure 13. Proportion of patients who received prior treatment with immunosuppressants or phototherapy with an improvement in WI-NRS (≥4 points) and IGA PN-S 0 or 1 (pooled analysis; post-hoc analysis)(68)



IGA PN-S = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Stage; WI-NRS = worst-itch numeric rating scale

B.2.8 Meta-analysis

Pooled efficacy results from PRIME2 and PRIME are presented in Section B.2.6. The SLR did not identify any additional relevant studies on the efficacy of dupilumab in patients with PN (Appendix D). Therefore, no additional meta-analyses were conducted.

B.2.9 Indirect and mixed treatment comparisons

There are currently no licensed or NICE-recommended targeted systemic treatments for PN aside from dupilumab. Moreover, there is a lack of RCT evidence to support the use of current off-label treatments. Given the expectation for the use of dupilumab for moderate-to-severe PN that is inadequately controlled on topical prescription therapies or when those therapies are not advisable, the most relevant comparator is BSC (defined as a combination of emollients, mild-to-moderate potency TCS/TCIs and rescue therapy).

As described in Section B.2.1Identification and selection of relevant studies, an exhaustive SLR was conducted to identify sources of clinical efficacy and safety evidence to allow indirect comparisons to be made (see Appendix D for further details on methods and results).

However, the majority of studies of comparator treatments that were identified were of low quality (i.e., non-RCTs with small sample sizes). Additionally, there was a lack of commonality between studies in terms of outcomes measures, which resulted in

heterogeneity in the reporting of efficacy in the treatment of PN. In particular, phototherapy studies identified in the SLR searches included ≤44 patients with PN and the only identified studies investigating cyclosporine and methotrexate were non-RCTs with ≤14 patients. While targeted systemic therapies are currently being investigated and the standardisation of efficacy endpoints is ongoing, indirect and mixed treatment comparisons were not at this time considered feasible to compare dupilumab against the comparators listed in the scope of the submission.(69)

B.2.10 Adverse reactions

The pooled analysis of safety outcomes for dupilumab in patients with PN included data from all treated patients in PRIME2 and PRIME at the primary cut-off dates for these studies (12 November 2021 and 30 August 2021, respectively).(54) All safety analyses were descriptive and performed on the safety population.(51, 52)

B.2.10.1 Overview of adverse reactions

Dupilumab was well tolerated and had a favourable safety profile in patients with PN (Table 13.).(54) The safety of dupilumab observed in PRIME2 and PRIME was consistent with the established safety profile of dupilumab in other indications (see Section B.2.12).

In the pooled safety analysis, 97 (63.8%) patients in the dupilumab group and 89 (56.7%) patients in the BSC group experienced ≥1 TEAE.(54) The majority of TEAEs were mild or moderate in intensity.(54) Severe TEAEs were reported in five (3.3%) patients in the dupilumab group and nine (5.7%) patients in the BSC group. Treatment emergent serious AEs (SAEs) were reported in seven (4.6%) patients in the dupilumab group and 12 (7.6%) patients in the BSC group.(54) [redacted].(51, 52)

The number of TEAEs considered by investigators to be related to IMP in the pooled safety analysis was [redacted] in the dupilumab group compared to [redacted] the BSC group.(54) No patients in the dupilumab group and four (2.5%) patients in the BSC group discontinued treatment due to TEAEs.(54) [redacted].(54) No patients in either treatment group died during the study.(54)

Table 13. Summary of AEs (Safety population; pooled analysis)(54)

	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
Treatment emergent AESI, n (%)	[redacted]	[redacted]
Treatment emergent other selected AE, n (%)	[redacted]	[redacted]
TEAE related to IMP, n (%)	[redacted]	[redacted]

AE = adverse event; AESI = adverse event of special interest; BSC = best supportive care; IMP = investigational medicinal product; SAE = serious adverse event; TEAE = treatment emergent adverse event

B.2.10.2 TEAEs

The most commonly reported TEAE (≥10% in either treatment group) in the pooled safety analysis were [redacted] (Table 14.).(54) [redacted] were also the most common TEAE reported in both treatment groups in PRIME2 and PRIME.(51, 52)

At the system organ class level, the incidence of TEAEs was generally similar across treatment arms. However, [redacted] were reported more frequently in the dupilumab group than in the BSC group in the pooled safety analysis.(54)

- For musculoskeletal and connective tissue disorders, the difference was due to a numerically higher number of patients in the dupilumab group who experienced TEAEs within the 'joint disorders' high level term of the Medical Dictionary for Regulatory Activities compared to BSC [redacted]. Both events of arthralgia were nonserious and mild, and none led to permanent study intervention discontinuation.
- The difference in gastrointestinal disorders was driven by the incidence of diarrhoea as a preferred team event.

[redacted].(54) TEAEs with a ≥1% greater incidence in the BSC group than in the dupilumab group were coronavirus disease 2019 (COVID-19), [redacted].(54) [redacted].(51)

Table 14. Summary of TEAEs (Safety population; pooled analysis)(54)

Primary system organ class Preferred term, n (%)	BSC (N=157)	Dupilumab (N=152)	Dupilumab vs. BSC RR (95% CI)
Any event	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Nasopharyngitis	3 (1.9)	6 (3.9)	2.02 (0.52, 7.83)
Conjunctivitis	[redacted]	[redacted]	[redacted]
COVID-19	5 (3.2)	1 (0.7)	0.21 (0.03, 1.72)
Folliculitis	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Headache	9 (5.7)	8 (5.3)	0.92 (0.36, 2.32)
Dizziness	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]
Conjunctivitis allergic	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Neurodermatitis	11 (7.0)	4 (2.6)	0.37 (0.12, 1.14)
Eczema	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Accidental overdose	[redacted]	[redacted]	[redacted]

BSC = best supportive care; CI = confidence interval; COVID-19 = coronavirus disease 2019; NC = not calculated; RR = relative risk; TEAE = treatment emergent adverse event

B.2.10.3 AESIs and other selected AEs

In the pooled safety analysis, [redacted] patient in the dupilumab group [redacted] and [redacted] patients in the BSC group [redacted] (Table 15.).(54) Other selected AEs that occurred less frequently in the dupilumab group than in the BSC group in the pooled safety analysis were [redacted].(54)

No cases of [redacted] were reported in either of the intervention groups in either of the PRIME2 or PRIME trials.(51, 52,

54) There were also no reports of [redacted] in either trial.(51, 52, 54)

Table 15. Summary of AESIs and other selected AEs (Safety population; pooled analysis)(54)

AE Category, n (%)	BSC (N=157)	Dupilumab (N=152)
Any treatment emergent AESI	[redacted]	[redacted]
Anaphylactic reactions (medically reviewed)	[redacted]	[redacted]
Systemic hypersensitivity reactions (medically reviewed)	[redacted]	[redacted]
Helminthic infections	[redacted]	[redacted]
Any severe type of conjunctivitis	[redacted]	[redacted]
Any severe type of blepharitis	[redacted]	[redacted]
Keratitis	[redacted]	[redacted]
Clinically symptomatic eosinophilia	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]
Significant ALT elevation	[redacted]	[redacted]
Symptomatic overdose with IMP	[redacted]	[redacted]
Symptomatic overdose with NIMP	[redacted]	[redacted]
Other selected AEs	[redacted]	[redacted]
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	[redacted]	[redacted]
Severe or serious infection	[redacted]	[redacted]
Drug-related hepatic disorder	3 (1.9)	0
Injection site reaction	9 (5.7)	6 (3.9)
Malignancy	2 (1.3)	1 (0.7)
Suicidal behaviour	[redacted]	[redacted]
Conjunctivitis (narrow CMQ)	2 (1.3)	6 (3.9)
Conjunctivitis (broad CMQ)	[redacted]	[redacted]
Conjunctivitis cluster[a]	[redacted]	[redacted]
Keratitis cluster[b]	[redacted]	[redacted]

AE = adverse event; AESI = adverse event of special interest; ALT = alanine transaminase; BSC = best supportive care; CMQ = customised MedDRA query; IMP = investigational medicinal product; NIMP = non-investigational medicinal product

[a] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation and eye inflammation.

[b] Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis and ophthalmic herpes simplex.

B.2.11 Ongoing studies

There are no ongoing Sanofi led studies for dupilumab in PN.

B.2.12 Interpretation of clinical effectiveness and safety evidence

The challenges in achieving PN disease control are driven by the lack of approved targeted systemic treatments for patients with moderate-to-severe PN, the absence of established treatment guidelines and limited RCT data on patient response to therapy.(4, 5, 18-20)

Treatment options are limited to topical treatments (e.g., TCS and UV phototherapy) and off-label systemic therapies (e.g., immunosuppressants, gabapentinoids, antidepressants and

thalidomide), which are associated with limited effectiveness and AEs.(15-18, 20, 22, 23) Moreover, phototherapy is not universally accessible to patients with PN due limited availability.(45) However, medically-complex patients with comorbidities affecting liver or renal function have even more limited treatment options aside from phototherapy due to many PN therapies being metabolised via the liver or kidneys (including cyclosporine and methotrexate) and potential drug-drug interactions.(25, 26, 70, 71) Given the majority of patients do not experience sufficient treatment efficacy from phototherapy alone,(48) there is an unmet need for alternative systemic therapies. Patients and clinicians require alternative, efficacious and well tolerated treatment solutions to address the multi-modal aetiology of PN, reduce the burden of itch and lesions and improve HRQoL.(18, 19, 23)

Data used to support the efficacy and safety of dupilumab in PN for this submission were taken directly from the randomised, double blind, phase III PRIME2 and PRIME trials which are the largest PN clinical trials conducted to date and represent the best available evidence to address the decision problem.(51, 52) PRIME2 and PRIME had similar study designs but differed only in the timing of their primary endpoints and locations, with almost one half of PRIME2 sites being in the European Union (including one site in the UK) while PRIME sites were mostly located in North America and Rest of World.(53) Results from PRIME2 and PRIME were pooled as part of a prespecified protocol to increase the statistical power of efficacy and safety analyses; this approach was appropriate due to the near identical nature of the studies and because there were no significant differences between study outcomes.(53) Overall, [redacted] of patients included in the pooled ITT analysis of PRIME2 and PRIME were enrolled from the European Union.(53) The PRIME2 and PRIME populations were also confirmed to represent the UK PN population by a UK dermatology expert who participated in an advisory board conducted by Sanofi in April 2022.(63) Data generated from PRIME2 and PRIME are considered generalisable to the UK based on the EADV consensus statement published in 2018, which showed clinician-reported treatment practices in the European Union are aligned with the UK (see Section B.1.3).(15)

Results from both the pooled ITT analysis and individual pivotal phase III studies demonstrated the efficacy and tolerability of dupilumab versus BSC in improving the symptoms of PN.(53, 54) Statistical significance was achieved for the primary endpoint of both individual studies as measured by reduction in WI-NRS by ≥4 points.(51-53) In the pooled analysis, the proportion of patients who achieved weekly average reduction of WI-NRS by ≥4 was two times greater in the dupilumab group than in the BSC group at Week 12 and three times greater at Week 24 (nominal $p<0.001$ for both).(53) Furthermore, the proportion of patients in the dupilumab group with reduction in WI-NRS by ≥4 points in the

pooled analysis was greater at Week 24 (58.8%) than at Week 12 (40.5%), suggesting dupilumab provides continuous and clinically meaningful improvement in itch.(53)

The individual PRIME2 and PRIME studies also reported more patients in the dupilumab groups with reduction in WI-NRS by ≥4 points at Week 24 than at Week 12, further demonstrating that the efficacy benefits of dupilumab continue to improve over time.(51, 52) This observation is consistent with results from the Sanofi-sponsored dupilumab AD open-label extension (OLE) study (Appendix T) which enrolled and treated 2,677 patients with moderate-to-severe AD with dupilumab. In this extension trial, key efficacy outcomes (i.e., Eczema Area and Severity Index and Peak Pruritus NRS) improved continuously from Week 2 to Week 24 and improvements (including in HRQoL) were observed up to Week 204. Therefore, it is likely that in the longer-term the efficacy benefits of dupilumab in PN will continue beyond Week 24.(55, 72)

Key secondary endpoints were also met across both studies and in the pooled analysis.(53) The proportion of patients in the pooled ITT analysis with healing PN skin lesions (IGA PN-S score of 0 or 1) and concomitant improvement in itch and skin lesions (WI-NRS reduction by ≥4 points and IGA PN-S score of 0 or 1) at Week 24 in the dupilumab group was significantly greater than in the BSC group.(53) Treatment with dupilumab significantly improved HADS total score, HADS-A and HADS-D from baseline to Week 24 compared to BSC (nominal p≤0.05 for all), which is an important patient-reported outcome given [redacted] and [redacted] of patients in the pooled analysis had at least borderline anxiety and depression at baseline, respectively.(53)

In addition, dupilumab provided significantly greater improvement in HRQoL (measured by DLQI), skin pain (measured by Skin pain-NRS) and sleep quality (measured by Sleep-NRS) compared to BSC in the pooled analysis.(53) Overall, the individual PRIME2 and PRIME studies also demonstrated a statistically significant benefit of dupilumab over BSC as assessed using secondary efficacy endpoints.(53) Based on results from a structured expert elicitation (SEE) study conducted by Sanofi in 2022, PN clinicians in the UK expect HRQoL improvements associated with dupilumab response to be maintained post-trial in patients who continue to receive treatment.(73) By comparison, HRQoL improvements in the BSC group are expected to wane quickly in post-trial, real world clinical practice setting.(73)

Treatment with dupilumab was well tolerated in patients with PN in the PRIME2 and PRIME studies.(54) In the pooled safety analysis, 63.8% experienced at least one TEAE, of which the majority were mild or moderate in intensity and only [redacted] were considered to be related

to treatment.(54) No patients in the dupilumab group discontinued treatment due to TEAEs compared to four patients in the BSC group and no new safety signals were identified.(54) Among patients with PN the frequency of conjunctivitis is [redacted],(54) though lower than that observed in AD patients with dupilumab (8.6% to 22.1%).(74) Moreover, there were [redacted] in the PRIME2 and PRIME trials.(51, 52, 54) A clinician's guide to recognition and management of dupilumab-associated conjunctivitis published in 2019 in response to the AD experience noted it is uncommon for patients to discontinue or reduce the frequency of dupilumab treatment in response to conjunctivitis and concluded that conjunctivitis is generally manageable.(75)

Data from PRIME2 and PRIME are generally consistent with existing safety data in patients with asthma, AD and CRSwNP.(55-59) Cumulative safety information for dupilumab is provided by the latest edition of the Periodic Benefit Risk Evaluation Report received by Sanofi's Global Pharmacovigilance department from worldwide sources.(76) At the Periodic Benefit Risk Evaluation Report cut-off date (28 March 2022) the number of patients exposed to dupilumab in clinical studies was 10,828.(76) This is now approximately 12,000 as studies continue to recruit.(55-59) Over 500,000 patients have been treated with dupilumab and as of March 2022 the estimated cumulative patient exposure for all dupilumab treated patients in clinical practice was 706,212 patient years.(76, 77) The important identified risks for dupilumab are "systemic hypersensitivity" and "conjunctivitis and keratitis related events in atopic dermatitis patients", while the only important potential risk is "eosinophilia associated with clinical symptoms in asthma patients".(76)

The results of an open-label study of patients with moderate-to-severe AD found dupilumab to be effective and well tolerated at three-year and four-year follow-up, with rates of conjunctivitis that were consistent with the phase III clinical trial.(55, 78) This is aligned with results from an investigator-initiated SLR and meta-analysis conducted to assess the real-world efficacy and safety of dupilumab in patients with AD across 22 studies (N=3,303); overall, the real-world safety profile of dupilumab was comparable to those observed in the clinical trial safety data.(79)

Based on the evaluation of the cumulative safety data and the benefit-risk analysis during the reporting interval, the benefit-risk balance of dupilumab across all indications remains positive in the currently approved conditions of use.(76) This consistent benefit risk ratio of dupilumab in PN and the other approved type 2 inflammation indications could have important implications for treatment given that approximately 50% of patients with PN are

diagnosed with an atopic predisposition (most commonly AD) and 26% of the atopic patients with PN present with AD plus asthma and/or allergic rhinitis.(15) Therefore, it can be concluded that dupilumab has favourable long-term safety and tolerability and is associated with mostly mild or moderate TEAEs, a low rate of treatment discontinuation and a low rate of serious TEAEs.

The number of patients included in PRIME2 and PRIME is primarily driven by the low prevalence of PN, which is considered a rare disease in the UK (prevalence of 3.27 per 10,000 in England; see Section B.1.3).(10, 11) Patients with severe renal conditions and drug-induced PN were excluded in the PRIME2 and PRIME studies to avoid confounding improvement in other uncontrolled systemic diseases and comorbidities with improvements in symptoms of PN. Similarly, patients aged >80 years of age were excluded to avoid mistakenly enrolling patients with Willian's itch, a common cause of pruritis in the elderly that is hard to differentiate from PN.(80)

A combined total of 311 patients (n=153 received dupilumab) were randomised in PRIME2 and PRIME, which represent the largest high-quality RCTs in PN.(53) This number of participants was considered sufficient to demonstrate the benefit of dupilumab in patients with PN given the existing safety database in patients with asthma, AD and CRSwNP; the PRIME2 and PRIME studies were accepted by the European Medicines Agency and MHRA as sufficient evidence for approval of dupilumab in patients with PN. While only one trial site was located in the UK, results from PRIME2 and PRIME can be generalised to the UK given that 54.2% of patients in the pooled dupilumab group were White.(53) The PRIME2 and PRIME populations were also confirmed to represent the UK PN population by a UK dermatology expert who participated in an advisory board conducted by Sanofi in April 2022.(63) Overall, the efficacy and safety of dupilumab in PN has been demonstrated in PRIME2 and PRIME and is further supported by clinical trial outcomes in several other approved indications.(53, 55-59)

Subgroup size was reflective of the epidemiology of PN, which as a rare disease poses challenges for interpretation. Nevertheless, subgroup analyses have demonstrated that dupilumab is efficacious regardless of disease characteristics (atopy, duration of PN), PN severity (IGA PN-S) and prior treatment (TCS/TCI, immunosuppressants, antipruritics).(53) Although efficacy was not estimable for a number of pre-specified subgroups which contained less than 50 patients (including age: ≥65 to >75 years, age: ≥75 years, race: Black/African descent, race: others, disseminated or localised PN lesions: ≤two BSA and phototherapy use: yes) there is no a priori clinical reason why dupilumab efficacy would be

different in these subgroups.(53) This assumption is supported by two case series of patients with Black/African descent, in which patients who did not respond to various prior therapies (including TCS, phototherapy, antihistamines and methotrexate) experienced a reduction in PN symptoms following treatment with dupilumab.(81, 82)

The main limitation of the dupilumab studies in the PN evidence base is the duration of monitoring of the study population in the clinical trials. In the individual PRIME2 and PRIME studies, the primary endpoint (proportion of patients with WI-NRS improvement (reduction) by ≥4 points from baseline) was measured at 12 weeks and 24 weeks, respectively, in line with regulatory requirements, with key secondary and other secondary endpoints being measured up to 24 weeks. However, those patients with the greatest potential to achieve benefit may require a longer treatment to reach the optimal effect as entrenched skin lesions can take a significant amount of time to heal.(51, 52) The prolonged long-term effect of dupilumab has been shown by the results of the OLE study in patients with moderate-to-severe AD where improvements in key efficacy outcomes and HRQoL were observed up to Week 204 (n=352; number of patients who completed up to Week 204 of treatment).(55, 72) While currently there are no results from long-term follow-up for the sustained benefit of dupilumab in PN, the results of the SEE study (Section B.3.3.2.2.4) conducted by Sanofi in 2022 (with clinicians familiar with both PN and dupilumab) in combination with reported outcomes in several other approved indications for dupilumab, indicate that the benefits of dupilumab in patients with moderate-to-severe PN can be assumed to extended beyond Week 24.(53, 55-59, 73)

In conclusion, dupilumab provides sustained, clinically and statistically significant improvements of PN signs, symptoms, as well as HRQoL, while having an acceptable safety profile. UK dermatologists who participated in advisory boards conducted by Sanofi in 2022 consider the 24 week results to be *'impressive'* and expressed an interest in using dupilumab in their PN patient groups.(63) Dupilumab has an acceptable risk-benefit profile in patients with PN uncontrolled on topical prescription therapy with no laboratory monitoring requirements. Dupilumab can generate a significant step change in the treatment trajectory of patients with PN, providing meaningful benefits to a burdened patient population with very limited treatment options.

B.3 Cost effectiveness

Model Overview

- A cost-effectiveness analysis was conducted to evaluate dupilumab plus BSC in comparison to BSC alone from the perspective of the National Health Service (NHS) in England for the treatment of PN.
- Following review of the literature and preceding relevant technology appraisals, a cost-utility model consisting of a 24-week decision tree followed by a three-state Markov model (cycle lengths are 12-weeks over a lifetime horizon) is presented in this submission.
    - Population: adults with moderate-to-severe PN whose disease is inadequately controlled with topical prescription therapies or for whom these therapies are not advisable.
    - Model inputs: clinical efficacy data for the base case are from the LIBERTY trial programme (PRIME2 and PRIME trials). HRQoL data are based on directly observed trial data. Resource utilisation data and unit costs are based on UK clinician opinion and published UK cost data.
- The base-case response criterion was WI-NRS improvement ≥4 from baseline and IGA PN-S score ≥1 from baseline at Week 24.
- In the absence of extension studies to inform long-term treatment in PN, committee-accepted assumptions from previous NICE appraisals in AD and results from a SEE (scenario analysis) were used as the basis for response waning and long-term treatment effect in the model, respectively.
- Utility was based on the EuroQoL five-dimension five-level (EQ-5D-5L) data directly collected in PRIME2 and PRIME, which was derived directly from patients with PN, and valued using the UK tariff.
- Resource use data for responders and non-responders were selected based on clinician input provided during an advisory board; Sanofi retrospective burden of illness (BOI) study in England for hospitalisation; and previous appraisals for dupilumab in AD for other costs.

Results

- Dupilumab was associated with a base case incremental cost-effectiveness ratio (ICER) of £26,886 per quality-adjusted life-year (QALY) gained.
- Results were driven by baseline utility, change in utility, and response waning.
- These results were consistent in all scenario and sensitivity analyses conducted indicating low decision uncertainty.

Benefits not captured in the QALY calculation

- Dupilumab offers significant benefits to patients and society that are not captured in the QALY. Social functioning is not included in the descriptive system in EQ-5D but is an important aspect of disease burden. Importantly, it may have significant impact on

productivity, which is explored in sensitivity analysis and captured in the model as indirect costs.

Conclusions

- Dupilumab is a clinically- and cost-effective use of NHS resources in patients with moderate-to-severe PN. This is a small group of patients and so a low budget impact from the adoption of dupilumab for this rare disease is anticipated. The clinical evidence and economic analysis highlight that dupilumab would address significant unmet need for adult patients with inadequately controlled PN who are candidates for systemic therapy.

B.3.1 Published cost-effectiveness studies

B.3.1.1 Systematic literature review

An economic SLR was conducted to identify studies assessing the HCRU, costs, utilities and cost-effectiveness of dupilumab or other treatments for PN. There was no lower limit on time horizon for database searches and the cut-off date for articles included in the economic SLR was 16th December 2022. Full details of the economic SLR methodology, study selection process, inclusion and exclusion criteria and results are presented in Appendix G.

The SLR identified no appropriate precedents for economic evaluations or economic models of treatments for PN. One study by Whang et al. 2021 sought to quantify the economic burden of PN using the average QALYs lost and individual lifetime cost burden.(83) However, this study was not suitable to inform the model for this pharmacoeconomic assessment because (i) the study was conducted in the US and (ii) overall QALY loss was estimated using a regression analysis and Health Utilities Index Mark 3 (HUI3) data, which does not provide inputs aligned with the model structure or the multiple health states in our proposed economic model.(83) The lack of available economic model data for PN led us to consider model structures from other related dermatological conditions, such as AD and pruritus, as supported by clinical experts in advisory boards conducted in 2022 (Section B.3.1.3).(1, 63)

B.3.1.2 Supplementary targeted literature review

An additional targeted literature review (TLR) was conducted for pruritus (itch), a condition that can be considered relevant to PN, because pruritus is one of the most common symptoms in PN and contributes to the pathophysiological cycle (Section B.1.3.1). Moreover, the purpose of interventions in PN is to reduce itch (Section B.1.3.2).

The TLR only identified one economic analysis of potential interest that was conducted by van Os-Medendorp et. al., evaluating the costs and cost-effectiveness of interventions used to manage chronic pruritus.(84, 85) The model contains only two health states: 'Receiving the intervention (cognitive behavioural interventions)' versus 'Receiving usual care'.(85) Thus, the treatment arm is used as a proxy for the health state, indicating that receiving treatment coincides with the key clinical event experienced by patients with pruritus.(85)

The model's characteristics and results are summarised in Table 16. However, given that i) the patient pathway, disease natural history and outcomes for PN would not be adequately captured using this simple two-state model and ii) that biologic treatments were not included as a comparator, this model structure was deemed inappropriate for the scope of this assessment.

Table 16. Summary of the published cost-effectiveness study of pruritus(85)

Study	van Os-Medendorp et al.
Year	2008
Summary of model	CEA using information from the trial 'Coping with Itch', which evaluated the clinical effectiveness of a nursing programme for patients with chronic pruritic skin diseases. While the type of model was not reported, patients were assigned to one of two health states: behavioural interventions with usual care (according to the 'Coping with Itch' programme) vs. usual care alone, and had a time horizon of nine months (the same as the trial duration). The CEA was performed from a societal perspective. The currency year was not reported.
Patient population	• Individuals with chronic pruritic skin diseases, regardless of underlying diagnosis • Recruited by tertiary care dermatologists • >18 years of age
QALYs (intervention, comparator)	QALYs: NR Intervention(s): 'Coping with itch' (i.e., nurse-led educational and cognitive behavioural interventions[a]) + usual care[b] Comparator(s): usual care (emollients + topical corticosteroids)
Costs (currency) (intervention, comparator)	GP; Dermatology outpatient; Other healthcare professional; Hospitalisation days; Medication use; Days off work
ICER[C] (per QALY gained)	At month 3: €129.90; At month 9: €16.60

CEA = cost-effectiveness analysis; GP = general practitioner; ICER = incremental cost-effectiveness ratio; NR = not reported; QALYs = quality-adjusted life years
[a]Including individual patient education, awareness training and habit reversal and relaxation exercises.
[b]Usual care not defined beyond 'medical care from a dermatologist'.
[c]ICER is expressed as incremental cost per gained day with a low frequency of itch.

B.3.1.3 Economic models from previous NICE assessments

As part of our efforts to identify an appropriate modelling approach, several economic models developed for previous technology appraisals were considered. As examples of accepted best practice, we summarise three models from previous NICE appraisals (TA534, TA681, TA814) which evaluated the cost-effectiveness of treatments for AD. PN and AD are similar chronic, type 2 inflammatory skin diseases requiring long-term management in which

assessment for treatment response to biologic therapy is expected three to six months following treatment initiation. The two diseases have a comparable impact on patient HRQoL.(86)

A model was previously developed to assess the cost-effectiveness of dupilumab in the treatment of AD. This was appraised by the NICE committee in August 2018 and a positive recommendation made (NICE TA534).(2) The model used a 52-week decision tree reflecting the trial evidence followed by a Markov model for long-term treatment.(2) Patients entering the decision tree were assigned to dupilumab or BSC. At 16 weeks, responders to dupilumab continued treatment with dupilumab (for up to 52 weeks), while dupilumab non-responders switched to BSC.(2) At Week 52, patients who continued responding to dupilumab entered the Markov model under a 'maintenance treatment state' while all non-responders entered under the 'BSC state'.(2) The Markov segment modelled long-term treatment with a lifetime time horizon (up to 61 years) and used three treatment states with a cycle length of 12 months each: maintenance treatment, BSC and death (Table 17).(2)

A similar approach was also used in the NICE appraisal of baricitinib for AD (NICE TA681, March 2021), where a 52-week decision tree was used in combination with a Markov model containing four treatment response states: induction, maintenance, non-response and death (Table 17).(87)

The approach taken in TA534 has been followed, with minor modifications, for the evaluation of all subsequent appraisals for AD. These include abrocitinib, tralokinumab or upadacitinib for the treatment of moderate to severe AD (NICE TA814, August 2022).(88) The approach used a 52-week decision tree, the results of which fed into a long-term Markov model for the rest of lifetime horizon (Table 17).(88)

Table 17. Summary of previous cost-effectiveness models used to evaluate treatments for AD(2, 87, 88)

Technology appraisal	TA534 Dupilumab for treating moderate to severe AD	TA681 Baricitinib for treating moderate to severe AD	TA814 Abrocitinib, tralokinumab, or upadacitinib for treating moderate to severe AD
Publication date	1 August 2018	3 March 2021	3 August 2022
Summary of model	CEA informed by clinical trials (including an OLE study; Appendix T); Type of model: 52-week decision tree followed by a Markov model; Time horizon: 61 years; Treatment response states: dupilumab vs. BSC; Currency year: March	CEA informed by clinical trials; Type of model: 52-week decision tree followed by a Markov model; Time horizon: NR; Treatment response states: Baricitinib vs. dupilumab or BSC; Currency year: December 2020; Perspective: Healthcare system	CEA informed by NMA of relevant trials; Type of model: 52-week decision tree followed by a Markov model; Time horizon: Rest of lifetime; Treatment response states: Abrocitinib, tralokinumab, upadacitinib vs. BSC; Currency year: March 2022; Perspective: Healthcare system

Technology appraisal	TA534 Dupilumab for treating moderate to severe AD	TA681 Baricitinib for treating moderate to severe AD	TA814 Abrocitinib, tralokinumab, or upadacitinib for treating moderate to severe AD
	2018; Perspective: Healthcare system		
Patient population average age in years	38 years	NR (adult population)	NR (adult population)
QALYs (intervention, comparator)	Response was measured by the composite endpoint of EASI 50 plus an improvement in the DLQI of ≥4 Comparator: BSC	Response was measured by the composite endpoint of EASI 50 plus an improvement in the DLQI of ≥4 Comparator: BSC	Response was measured by the composite endpoint of EASI 50 plus an improvement in the DLQI of ≥4 Comparator: BSC
Costs (currency) (intervention, comparator)	Healthcare resource use data implemented in the base case have been taken from secondary care case notes review. Dermatology visits and specialist nurse visits were considered in the model and validated in an advisory board. Inputs have been validated with UK dermatologists, in particular, the number of hospitalisations, nurse attendances and A&E visits. Costs (GBP) included resource use for adverse events (injection site reactions, allergic conjunctivitis, infectious conjunctivitis and oral herpes).	Costs (GBP) for resource use were based on TA534; the committee preferred to omit the costs of bathing products from the model	Abrocitinib costs (GBP): Resource use assumptions taken from TA534 and TA681. Background medications were TCS, emollients and TCI (bathing products omitted). Tralokinumab costs (GBP): Resource use assumptions taken from TA534, BSC background medication costs included TCS, emollients and TCI (bathing products omitted). Upadacitinib costs (GBP): Resource use assumptions taken from TA534. Background medications included TCS, emollients, TCI and bathing products
ICER[a] (per QALY gained)	£27,410 to £28,495 per QALY gained	£27,037 to £28,396 per QALY gained	**Abrocitinib combination:** • 100 mg = £142,241 vs. dupilumab; £69,593 vs. baricitinib • 200 mg = £218,356 vs. dupilumab; £60,757 vs. baricitinib **Abrocitinib monotherapy** • 100 mg = £125,278 vs. dupilumab; £88,344 vs. baricitinib • 200 mg = £167,991 vs dupilumab; £53,040 vs. baricitinib **Tralokinumab combination:** • £115,545 vs. dupilumab; £26,969 vs. BSC **Tralokinumab monotherapy:** • £125,178 vs. dupilumab; £24,666 vs. BSC

Technology appraisal	TA534 Dupilumab for treating moderate to severe AD	TA681 Baricitinib for treating moderate to severe AD	TA814 Abrocitinib, tralokinumab, or upadacitinib for treating moderate to severe AD
			Upadacitinib + TCS – adult systemic eligible: • 15 mg = £13,173 vs CsA + TCS • 30 mg = £29,934 vs CsA +TCS **Upadacitinib + TCS – adult systemic exposed:** • 15 mg = £10,583 vs BSC; £128,057 vs. dupilumab + TCS • 30 mg = £25,163 vs BSC; dominant vs. dupilumab + TCS

AD = atopic dermatitis; A&E = Accident and emergency department; BSC = best supportive care; CEA = cost-effectiveness analysis; CsA = ciclosporin; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; GBP = Great British Pounds; ICER: incremental cost-effectiveness ratio; NMA = network meta-analysis; NR = not reported; OLE = open=label extension; QALY = quality-adjusted life year; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids

B.3.2 Economic analysis

B.3.2.1 Patient population

The economic analysis presented here is a cost-effectiveness analysis comparing dupilumab with BSC for the treatment of adults with moderate-to-severe PN who are candidates for systemic therapy. This represents the full expected licence indication (Section B.1.2 Description of the technology being evaluated).

- The patient population in the model was based on the cohorts included in the PRIME2 and PRIME trials.(51, 52) This is the base-case population for this economic analysis, in line with the anticipated position for dupilumab in UK clinical practice based on clinician feedback.(1)
- 'Inadequately controlled' refers to patients in the PRIME2 and PRIME trials who were unable to achieve and/or maintain remission and low disease activity (similar to an IGA-PN score ≤two, i.e., fewer than 20 nodules), despite treatment with a daily regimen of medium-to-super potent TCS (with or without add-on TCI as appropriate) applied for at least 14 days or the maximum duration recommended by the product prescribing information, whichever is shorter (see Section B.2.3.2 for trial eligibility).(51, 52)
- These patients have the highest unmet need for an effective treatment, as the only treatment option for them currently is BSC (Section B.1.3.2).

B.3.2.2 Model structure

In the absence of published economic model data for PN (Section B.3.1.1 Systematic literature review),(83) a de novo model was developed for PN based on the model structures previously developed in the analogous disease area of AD (Section B.3.1.3). This approach was supported by clinician input in advisory boards conducted in 2022.(1, 63) Microsoft Excel® was used to estimate the long-term cost-effectiveness of dupilumab compared to BSC which was defined as a combination of emollients, low-to-medium potency TCS/TCI and rescue therapy (such as higher potency topical or oral corticosteroids or TCIs). The model estimates costs and outcomes using a combined decision tree and Markov structure.

The model considers an NHS England perspective in which direct medical costs incurred by the NHS for PN treatment are compared, health benefits are compared, and resulting ICERs are generated. The model also has an option to include productivity costs to provide a societal perspective.

The model structure is designed to reflect UK clinical practice for PN. The structure of the model is divided into two sections. The model starts with a 24-week decision tree to reflect the dupilumab trials (Figure 14). This timeframe was informed by the key secondary and primary endpoints in the PRIME2 (WI-NRS ≥4 from baseline to Week 24) and PRIME (WI-NRS ≥4 from baseline to Week 24) trials, respectively (Section B.2.3.1 Trial design).

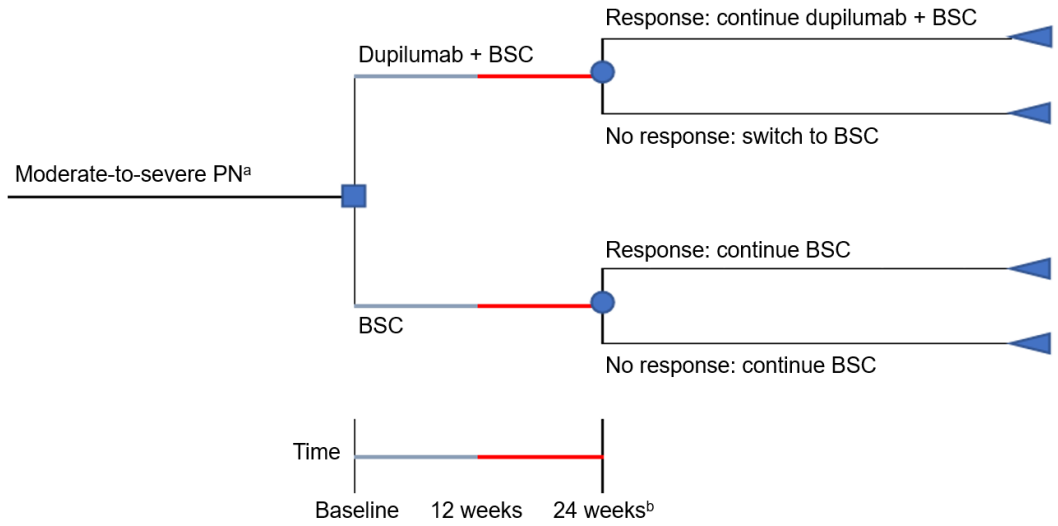
- After 24-weeks, patients are assessed for response to treatment according to the efficacy response criterion discussed in Section B.3.3 and if they are responding, they are assigned to continue receiving dupilumab plus BSC.
- If patients are not responding to dupilumab, they are assigned to receive BSC only.

The decision tree portion of the model is followed by a long-term Markov model structure which, similar to previous NICE appraisals in AD (Section B.3.1.3 Economic models from previous NICE assessments), uses treatment response states rather than health states. The model represents the remaining disease course applied over a lifetime time horizon, the Markov model's cycle length is 12 weeks. The combined decision tree and Markov state transition model was accepted as appropriate by previous committees assessing AD models for dupilumab (TA534), baricitinib (TA681) and abrocitinib, tralokinumab, or upadacitinib (TA814).(2, 87, 88)

Figure 14 presents the decision tree structure. Patients with moderate-to-severe PN are treated with either dupilumab plus BSC or BSC alone (shown by the blue decision node; Section B.2.3.1 Trial design). At the first assessment point at Week 24 (shown by the blue chance nodes), a clinical check is performed to determine the response in both arms.

- The proportion of patients responding to treatment in the model is determined by efficacy criterion applied to the clinical trial data in each arm. This is further discussed in Section B.3.3.
- Immediately after the Week 24 assessment (according to the efficacy response criteria discussed in Section B.3.3) patients leave the decision tree and are moved to the Markov model. They enter the Markov model in the treatment response state that fits the outcome of their clinical assessment. That is, responders enter the Markov model in the 'Response' treatment state, and non-responders enter the Markov model in the 'No response' treatment state (Figure 15).
- Patients receiving BSC alone upon entering the model do not discontinue BSC regardless of the response status, but utility and costs in BSC do differ by response status.
- Patients receiving dupilumab plus BSC upon entering the model discontinue dupilumab if they are non-responders and continue on BSC only so that utility and costs in the dupilumab plus BSC treatment arm differ by response status.

Figure 14. Decision tree structure

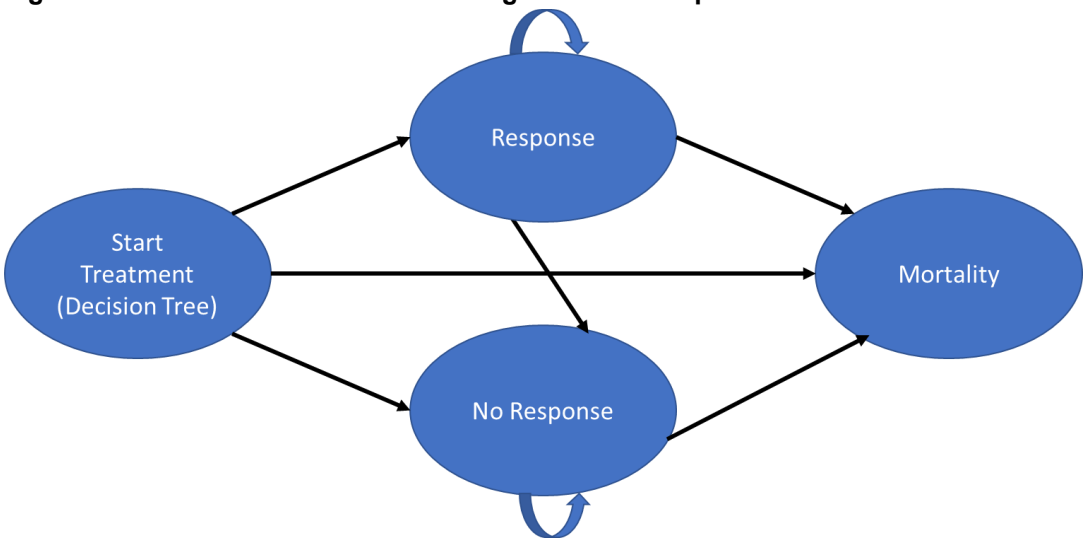


BSC = best supportive care; PN = prurigo nodularis.
[a]Moderate to severe PN is defined as prurigo nodularis inadequately controlled with topical prescription therapies or when these therapies are not appropriate.
[b]The clinical assessment timepoint in the PRIME2 and PRIME trials was 24 weeks.

All patients are at an equal risk of general mortality, which is not affected by PN.

Patients in the 'Response' treatment state persist on treatment until discontinuation due to loss of response, AEs or patient/clinician preference. After discontinuation, these patients move to the 'No response' treatment state. The patients in the 'No response' treatment state receive BSC treatment alone.

Figure 15. Markov model structure using treatment response states



The base-case analysis used a lifetime horizon (or until patients reach the age of 100 years). The lifetime horizon aims to capture the potential impact on costs and outcomes over a patient's lifetime, which is consistent with the NICE reference case.(89)

The cost-year of the analysis was 2022. Costs published for previous years were inflated to 2022 using consumer price inflation data from the Office for National Statistics, in line with NICE recommendation.(90)

In the base-case analysis, costs and outcomes were discounted at 3.5% according to the reference case.(89)

UK clinicians who participated in an advisory board (Section B.3.5.3 Advisory board to evaluate UK clinicians' perceptions of healthcare resource use) conducted by Sanofi in December 2022 endorsed the PN model structure. The clinicians acknowledged there is a chance some patients could temporarily achieve symptom improvement on systemic therapies, and thus move from the non-responder to responder treatment state for a short period of time. However, this treatment effect is expected to happen only in the short term and no long-term benefit is expected from treatment with systemic therapies. Thus, patients may move up from the 'No response' to 'Response' treatment state, but then will eventually revert to the 'No response' treatment state. While the model could have been designed with a treatment sequence structure that would represent these step-ups and subsequent step-down to non-response, the benefits of the systemic therapies are likely to cancel out and the overall benefit remain the same.

In addition, the clinicians thought it would be difficult to quantify the proportion of patients that would achieve temporary symptom improvement on systemic therapies, since they suggested that responses are highly variable in patients with PN.

Thus, there is a possibility of missing costs for non-responders in the comparator arm who could temporarily step up and potentially receive a more costly treatment for a period of time. Therefore, experts concluded that the model structure is conservative from a cost perspective and acceptable from a health technology assessment agency perspective.(1)

Similarly, the expert panel on a global advisory board conducted by Sanofi in April 2022 said that the settings used in the model are 'standard' and in line with expectations.(63)

B.3.2.3 Intervention technology and comparators

The intervention in the model was dupilumab plus BSC versus BSC alone for the UK target population. BSC in the economic model is based on the treatment regimens prescribed for the BSC arm in the PRIME2 and PRIME trials, where BSC is a combination of emollients, low-to-medium potency TCS/TCI and rescue therapy (such as higher potency topical or oral corticosteroids or TCIs).

Based on the results of an advisory board conducted by Sanofi in December 2022 with UK clinicians who treat patients with PN, there is no well-defined BSC for patients with PN (Section B.3.5.3 Advisory board to evaluate UK clinicians' perceptions of healthcare resource use).(1) Note that in the PRIME2 and PRIME trials, low-to-medium potency TCS/TCI was allowed if patients were on stable use prior to screening. A stable regimen for TCS or TCI was defined as the administration of the same medication (low-to-medium potency TCS/TCI) at the same frequency (once or twice daily) continuously starting from two weeks prior to screening. By allowing participants to use topical agents such as TCS/TCI as a background therapy (including moisturisers and TCS/TCI) and by maintaining a consistent frequency of use of these therapies, the program aimed to assess the efficacy of dupilumab in a real word context, while minimising the potential confounding of efficacy endpoints.(15) Access to super potent TCS/TCIs was available for patients during the trial as rescue therapy. Data generated from PRIME2 and PRIME are considered generalisable to the UK based on the EADV consensus statement published in 2018, which showed that clinician-reported treatment practices in the European Union are aligned with the UK (see Section B.1.3).(15)

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

Baseline characteristics used in the model are shown in Table 18 for the base-case population. The baseline characteristics (age, percentage male, weight and utility weight) were populated with data derived from the pooled analysis of the PRIME2 and PRIME trials, which define the reference point for patients.(53) As described in Section B.2.12

Interpretation of clinical effectiveness and safety evidence, data from the trials were pooled as part of a prespecified protocol to increase the statistical power of efficacy and safety analyses.(53)

Sex and mean age of the population were used to estimate the general all-cause mortality.(53) Sex, mean age, utility weight, WI-NRS score and DLQI score were combined and used to estimate the treatment response utility weights (see Section B.3.4 for a detailed description of the utility weight option in the model).(53) The baseline characteristics data for the overall patient population relevant to the economic model are presented in Table 18.

Table 18. Baseline characteristics of the base-case patient population

Parameter	Base case: overall patient population	Reference
Age, years, mean (SE)	49.5 (0.9)	(53)
Percentage of male patients, %	34.7	(53)
Body weight, mean kg (SD)	73.9 (17.9)	(53)
Baseline utility estimated based on the algorithm by Hernández Alava, 2020 mean, (SD)[a]	[redacted]	(91)
WI-NRS score, mean (SD)	8.493 (1.007)	(53)
DLQI score, mean (SD)	17.5 (7)	(53)

DLQI = Dermatology Life Quality Index; SD = standard deviation; SE = standard error; WI-NRS = The Worst-Itch Numeric Rating Scale
[a] See Section B.3.4 for further details.

B.3.3.2 Clinical parameters and variables

Clinical parameters which were included in the model are as follows:

- Response criteria
- Long-term treatment effect and response waning
- Annual discontinuation rates
- Mortality

B.3.3.2.1 Modelled efficacy response criteria

The efficacy response criteria define which patients continue on treatment or discontinue treatment and move to the 'No response' state in the model. In the PRIME2 and PRIME trials, response to treatment, as assessed by the primary endpoints, was defined by improvement in WI-NRS as shown in Table 19.

Table 19. Definition of response in the PRIME2 and PRIME trials with results of the pooled ITT population analysis(45, 46, 47)

Endpoint	BSC (N=158)	Dupilumab (N=153)	Nominal p value
Patients with WI-NRS improvement (reduction by ≥4 from baseline to Week 24), the primary endpoint for PRIME			
Responders, n (%)	30 (19.0)	90 (58.8)	<0.0001

BSC = best supportive care; WI-NRS = worst-itch numeric rating scale

Based on a user selection of response, the model is populated with data that represent the probability of achieving the selected response criteria for each model comparator. The base-case analysis used WI-NRS improvement ≥4 from baseline and IGA PN-S score ≥1 from baseline at Week 24 as the response criterion (Table 20).

This response criterion combines the primary endpoint from the PRIME2 and PRIME trials (WI-NRS improvement ≥4) which measures the intensity of itch, with IGA (IGA PN-S score ≥1)which assesses nodular lesion number and thickness.(51, 52). Use of this response criterion was supported by UK clinicians in the advisory board conducted by Sanofi in December 2022.(1, 63) While WI-NRS and IGA PN-S are not routinely used to assess response in current UK clinical practice, the tools are considered easy to implement by the clinicians we have spoken to and furthermore, they have stated that they would like to use these criteria more frequently.(1, 63) It was noted that if WI-NRS is included in NICE guidance and/or dupilumab is introduced in clinical practice, this tool would be used routinely. This has been the case for the use of the EASI score introduced on the implementation of the high-cost treatments in AD. It is worth noting that the composite endpoint of EASI 50 plus an improvement in the DLQI score of ≥4 for the assessment of response to AD treatment was considered to be the most appropriate holistic assessment of response during the original NICE assessment of dupilumab. This was because it combined both signs and symptoms with the impact on HRQoL. This is aligned with the approach taken here for PN which measures the impact on itch (the most important determinant of HRQoL in PN) and the signs due to nodules.(1, 63)

In addition to the response criteria selection, response data from the studies is further delineated using the 'as observed with multiple imputation' (as observed + MI) method. In

the ‘as observed + MI’ response method, patients requiring rescue treatment who met the designated response criteria were still counted as responders based on pooled data from the PRIME2 and PRIME trials (pre-specified analysis in the trial protocols).(53) These patients were censored in the trial primary endpoint analysis. It is important to include them in the modelling, because they continue to receive treatment and experience related costs and consequences both in the study and as they would in real world clinical practice. Table 20 presents the proportion of responders meeting each criterion for the base-case overall patient population. WI-NRS improvement ≥4 and IGA-PN-S reduction ≥1 is used as the base case, and WI-NRS improvement ≥4 is used in the sensitivity analysis.

Table 20. Week 24 response data inputs for the base-case patient population (as-observed + MI method)

Response criteria	Base-case: overall patient population	
	Dupilumab plus BSC, %	BSC, %
WI-NRS improvement ≥4 and IGA-PN-S reduction ≥1	[redacted]	[redacted]
WI-NRS improvement ≥4	[redacted]	[redacted]

BSC = best supportive care; IGA-PN-S = investigator global assessment for prurigo nodularis stage; MI = multiple imputation; WI-NRS = worst-itch numerical rating scale

B.3.3.2.2 Long-term treatment effect and response waning

The model is designed to estimate the long-term benefit of treatment beyond the extent of the observed trial evidence. As there are no extension studies to allow for estimation of the real-world effectiveness of dupilumab or BSC in PN, the probability of sustained response (and maintenance of HRQoL) must be extrapolated. The following text presents justification for our approach used in the submission for long-term treatment effect and response waning. We discuss the sources of evidence used to populate both the base case and sensitivity analysis.

B.3.3.2.2.1 Approach in previous NICE appraisals in analogous disease area

Long-term HRQoL has been recognised as a key area of uncertainty in previous NICE appraisals in the analogous disease area of AD. The loss of treatment response for patients with AD after exiting the controlled clinical trial environment has been explored and a methodology agreed in the series of AD appraisals carried out by NICE, including the single technology appraisals for dupilumab (TA534)(2) and baricitinib (TA681),(87) and in the multiple technology appraisal for upadacitinib, abrocitinib and tralokinumab (TA814) (Section B.3.1).(88) The economic models in these submissions used a priori approach to defining the decline in HRQoL based on the committee-preferred assumptions derived from TA534. This approach included the application of treatment waning assumptions to all treatments as

patients may lose response over time. The adopted parameters in these models have largely been informed by the assumptions accepted in TA534 which are predicated on:

- Improved adherence to treatment due to regular clinic visits as part of the trial programme
- Increased access to healthcare facilities and professionals as part of the trial programme
- Access to best and continuously optimised BSC, including timely rescue treatments.

B.3.3.2.2.2 Approach for PN

Like AD, PN is a chronic type 2 inflammatory skin disease in which patients are significantly affected by itch, and in the case of PN, also by physical appearance due to the impact of visible bleeding skin lesions (Section B.1.3.1.6).(15) Both of these factors severely impact patient HRQoL.

In the pooled analysis of the PRIME2 and PRIME trials, there was a high treatment response rate in both the BSC and dupilumab arms (Section B.2). At Week 24, [redacted] and [redacted] of patients in the dupilumab and BSC arms, respectively, met the chosen response criteria (WI-NRS improvement ≥4 and IGA-PN-S reduction ≥1).

In the model BSC responders accrue the BSC response utility and this continues to be applied at Week 24. However, it is improbable that this effect size for BSC alone would persist once patients have completed the trials and are outside the protocol-driven clinical trial setting where behaviours, particularly around the adherence to topical treatments, are mandated. Data to support this hypothesis are not available from the PRIME2 and PRIME trials.

In the absence of other evidence for sustained treatment effect in the PN therapy area and considering the modelling approach used in previous NICE appraisals in AD, we consulted with clinical experts to understand if patients with PN would maintain the HRQoL benefit over a longer period after returning to real-world clinical practice. A qualitative clinician interview (Section B.3.3.2.2.3) and an SEE (Section B.3.3.2.2.4; informed by the interview) were carried out to more robustly quantify the trial protocol-driven effect, in line with NICE guidance for the evaluation of unknown qualities.(73) While there is an absence of NICE methodological guidance concerning the extrapolation of non-time-to-event outcomes such as utilities, the NICE methods guide states that alternative scenarios should be routinely considered to examine treatment benefit in the extrapolated phase and these may include modelling reductions in benefit over the long-term.(92)

B.3.3.2.2.3 Qualitative clinical interview

A clinician interview was conducted to provide an overall understanding of possible approaches for estimating the long-term treatment effect and response waning in the PN model and to understand if an SEE would be valuable to inform the model. Input and assumptions generated in the interview were then tested in the SEE.(73)

Results from the interview suggested that it would not be possible to sustain the treatment effect from BSC on HRQoL at the levels observed in the PRIME2 and PRIME trials. It was noted that adhering to multiple corticosteroids on a daily basis is burdensome but under trial conditions, patients tend to be more energised and adherent to their treatment regimen. Hence, while most of the improvement in HRQoL would be maintained in patients who continue to respond to BSC within trial, a decrease in HRQoL is expected post trial on return to the real world clinical practice setting. It is therefore reasonable to assume that patients treated under current clinical practice will return to their previous worse health state post trial.(73)

The clinician stated that a faster decline in adherence to BSC in PN patients might be expected post trial compared to AD, with consequent rapid loss of trial-based benefit. It was noted that a small minority of participants may maintain some response because they learn from the trial and could be more rigorous with their adherence. Therefore, while loss of benefit will be observed universally across patients on BSC, some patients may maintain a proportion of the benefits after returning to real life. This supposition was tested in the SEE.(73)

As patients in the dupilumab arm of the PRIME2 and PRIME trials are also subject to the trial protocol, the clinician was also consulted about their view on the maintenance of treatment effect for dupilumab in the post-trial setting. Several observations were made (and subsequently tested in the SEE):(73)

- Unlike BSC, dupilumab response is derived from the clinical benefit of receiving an active biologic substance
- Long-term evidence for dupilumab from the AD OLE study (Appendix T) demonstrates maintained treatment effect and sustained (or even improving) HRQoL.

The clinician concluded that dupilumab response would be maintained post trial and that based on the open-label extension study data for AD and clinical experience, there is no reason to believe that the HRQoL of patients who continue to respond and remain on

dupilumab would decrease over time. These observations were tested in the SEE described below.(73)

B.3.3.2.2.4 Structured expert elicitation (SEE)

SEE was undertaken to elicit how HRQoL might evolve in the short and longer term (i.e., at six months, one year and ≥two years) for patients with PN, after they leave the protocol-driven environment of the PRIME2 and PRIME trials and return to current real-world clinical practice.(55) The time points were selected based on consultation with a clinical expert. Though waning was assumed to occur over a 5-year period in the NICE appraisal of dupilumab for AD (TA534), the expert noted that waning would take place over a shorter period in PN, primarily due to the greater challenges with adherence in this patient group.(55) Note that these time points in the SEE are shorter than those used in the model (i.e. up to Year 5+; Section B.3.3.2.2.5); however, as stated, the SEE time points were validated by clinicians at the time of study design.(55) As the SEE and model developed, our approach also evolved and the time points used in the model diverged from those in the SEE.(55) This was a necessary and pragmatic decision to align the data.(55) Response waning values were explored in sensitivity analyses (Section B.3.8), which demonstrate that the model is stable and not highly sensitive to changes in these values.(55)

The approach to elicitation for this study was in line with structured expert elicitation resources (STEER) guidance,(93) which is based on the York reference protocol,(94) using a variable interval method (bisection) for all quantities of interest. The bisection method elicits the 1st percentile (lower plausible limit), 99th percentile (upper plausible limit) and 50th percentile (median) for each quantity of interest. Rationales for these judgements were also elicited. This method has been cited by NICE as the preferred approach for SEE.(89)

Experts were recruited based on the following pre-determined eligibility criteria:(55)

- Clinicians based in England and Wales
- Substantial experience of treating patients with PN: minimum 10 years
- Willingness to participate
- Experts would ideally have both trial and post-trial experience, and therefore have a good understanding of potential trial effects versus treatment effects on HRQoL; however, having experience in both was not a requirement.

STEER guidance indicates that a minimum of five experts should be identified.(93) Communications with healthcare professionals were conducted in accordance with the

Association of the British Pharmaceutical Industry Code of Conduct. Six experts were invited, of whom four took part in the exercise. However, the analysis was based on answers from three experts only. Mathematical aggregation does not require experts to converge on a group distribution, thus allowing variability between experts to be reflected within and when clarifications were required but stopped after three attempts if no response was provided. Therefore, one clinician was lost in follow-up.(55)

The experts provided input on the maintenance of HRQoL benefits after trial completion at three distinct timepoints (six months, one year and ≥two years) for four populations of interest. The dupilumab responder whilst on treatment was not considered on the basis that their response would continue undiminished until discontinuation according to clinician input. At that point the waning of treatment effect was elicited (first patient group below):(55)

1. Dupilumab responders: adults with PN from the dupilumab arm of the PRIME2 and PRIME trials, who responded to treatment during the trial but subsequently discontinued treatment at some point after the end of the trial for any reason and returned to current real-world clinical practice

2. Dupilumab non-responders: adults with PN from the dupilumab arm of the PRIME2 and PRIME trials, who did not respond to treatment or lost their response by the end of the trial and immediately discontinued dupilumab on return to current real-world clinical practice

3. BSC responders: adults with PN from the BSC arm of the PRIME2 and PRIME trials, who responded to treatment during the trial, and returned to current real-world clinical practice after the end of the trial

4. BSC non-responders: adults with PN from the BSC arm of the PRIME2 and PRIME trials, who did not respond to treatment or lost their response by the end of the trial and returned to current real-world clinical practice

Results from the elicitation suggest that nearly all HRQoL benefits accrued within the PRIME2 and PRIME trials would be lost after leaving them for all BSC patients and for dupilumab patients who discontinued treatment though the rate of decline and plateau point are dependent on treatment arm and response (Table 21). The rate of decline would likely be faster in the BSC arm versus dupilumab arm and in non-responders versus responders. The plateau point was higher in responders versus non-responders. Differences in emotional state of mind (loss of hope), adherence to topical treatments and scratching behaviours were

noted as rationales for differences in expert judgements between treatment groups. Further, experts agreed that patients would be close to baseline, or worse (in the case of BSC non-responders), at the two years' post-trial period and beyond, as HRQoL would deteriorate in patients without active treatment for two years.(55)

Table 21. Proportion of utility maintained at each time interval in structured expert elicitation

Subgroup	Time point[a]	Median (50th percentile)	IQR (25th-75th percentile)	95% CrI (5th-95th percentile)
Dupilumab responders, %	**6 months**	38%	27%-48%	20-59%
	1 year	18%	14%-25%	10%-39%
	2+ years	9%	6%-12%	3-%16%
Dupilumab non-responders, %	**6 months**	20%	11%-25%	8%-42%
	1 year	5%	1%-13%	-2%-18%
	2+ years	0%	-7%-8%	-15%-13%
BSC responders, %	**6 months**	29%	22%-38%	16%-49%
	1 year	15%	12%-19%	5%-25%
	2+ years	9%	2%-14%	-2%-17%
BSC non-responders, %	**6 months**	10%	6%-16%	3%-20%
	1 year	1%	-1%-11%	-3%-16%
	2+ years	0%	-9%-6%	-12%-9%

BSC = best supportive care; CrI = credible interval; IQR = interquartile range
[a] For the dupilumab responders, this is the time-post-treatment discontinuation; for all other subgroups, this is the time-post-trial completion
Source: clinical expert elicitation(55)

For more detailed information on the SEE protocol and results refer to Appendix N.

B.3.3.2.2.5 Choice of data inputs

A combination of data and assumptions from previous NICE appraisals in the analogous disease area of AD (Section B.3.1.3 Economic models from previous NICE assessments) and results from the SEE were used as the basis for long-term treatment effect and response waning data in the PN model.

A summary of the accepted and most plausible waning values taken from the single technology appraisals for dupilumab (TA534)(2) and baricitinib (TA681),(87) and in the multiple technology appraisal for upadacitinib, abrocitinib and tralokinumab (TA814)(88) is provided in Table 22 (Section B.3.1.3).

Table 22. Summary of accepted waning values in previous AD NICE appraisals

Product and TA number	Most plausible analyses	Proportion of patients losing benefit, %			
		Year 2	Year 3	Year 4	Year 5+
Dupilumab TA534(2)	Dupilumab: From trial investigators based on their experience with dupilumab, supported by 100-week OLE study (see Appendix T for summary of study)	2	5	7	8
	BSC base case: Linear decline tested by EAG (NICE preferred option)	25	50	75	100

Product and TA number	Most plausible analyses	Proportion of patients losing benefit, %			
		Year 2	Year 3	Year 4	Year 5+
	BSC sensitivity analysis 1: From Weibull curve fitted to CHRONOS[a] KM data for time to first rescue treatment/study withdrawal (BSC arm)	82	90	94	96
	BSC sensitivity analysis 2: From annual rate of CHRONOS[a] time to first rescue therapy/study withdrawal (BSC arm)	57	82	92	97
Baricitinib TA681(87)	Baricitinib: From TA534	2	5	7	8[b]
	BSC base case: Between the EAG's approach (no waning, BSC modelled as a single treatment response state of 50% responders and 50% non-responders) and TA534 Sensitivity Analysis 2	0–57	0–82	0–92	0–97
Upadacitinib, abrocitinib & tralokinumab (TA814)(88)	All interventions: From TA534	2	5	7	8[b]
	BSC base case: Sensitivity Analysis 2 from TA534	57	82	92	97

AD = atopic dermatitis; BSC = best supportive care; EAG = external assessment group; KM = Kaplan-Meier; NICE = National Institute for Health and Care Excellence; OLE = open=label extension; TA = technology appraisal
[a]1-year clinical trial for dupilumab in moderate-to-severe AD.
[b]Based on experience with dupilumab in AD.

Using these data as a starting point, we adapted the assumptions to provide a set of inputs for the base case and scenario analysis in the PN model. These are discussed below and tabulated in Table 23 and Table 24.

❖ *Base case: maintenance of treatment effect in dupilumab*

In the absence of long-term data for dupilumab in PN and because high quality long-term data are available for AD, we use data from the dupilumab in AD open-label extension study in the base case (Appendix T) which demonstrates that use of dupilumab over the longer term is associated with maintained or indeed increased benefit (Section B.2.12

Interpretation of clinical effectiveness and safety evidence). This study provides the most robust data available and was noted as the preferred data for response waning with dupilumab in the global advisory board for PN conducted in April 2022 (Section B.3.5.3 Advisory board to evaluate UK clinicians' perceptions of healthcare resource use).(63)

❖ *Base case: maintenance of treatment effect in BSC patients*

For the base case in the BSC arm, we acted on the recommendations for BSC received from the NICE technical team and external assessment group (EAG) at the decision problem meeting (held on 17th November 2022) and have used the NICE committee's assumption from TA534. For this appraisal of dupilumab in AD, a brief survey of clinical experts was conducted to elicit the expected baseline utility values for both arms and the rate at which patients would return to that baseline. The basis of the argument is that it is improbable that

this effect size for BSC alone would persist once patients have completed the studies and are outside the protocol driven clinical trial setting where behaviours, particularly around the adherence to treatments, are mandated. Conversely the EAG found the resulting utility estimates used in TA534 to be implausible, instead suggesting that HRQoL would remain at the levels observed at the end of the trial indefinitely. The NICE Appraisal Committee felt that both of these scenarios were implausible, preferring a scenario where some patients maintained benefit from Year 5 and beyond. These values were used in subsequent technology appraisals (e.g., TA681).

❖ *Sensitivity analysis: maintenance of treatment effect in dupilumab*

For the sensitivity analysis in the dupilumab arm, we have used the NICE-accepted data from TA534 (Table 22 above) which state that 98% of dupilumab patients would maintain benefit at two years, 95% retain benefit at three years, 93% retain benefit at four years and 92% retain benefit at five+ years. This translates into the within-year conditional proportion of remaining patients with maintenance of benefit shown in Table 23.

❖ *Sensitivity analysis: maintenance of treatment effect in BSC patients*

For the sensitivity analysis in the BSC arm, the model includes parameters for waning of response based on the SEE. As discussed in Section B.3.3.2.2.4, the elicited expert responses indicate an expected return to a lower HRQoL very quickly for PN patients treated with BSC, much faster than for AD. The responses also suggest that some patients will continue to receive benefit, likely due to improved adherence beyond two years. In order to model this, we have carried forward the response elicited for Year 3.

We were asked by NICE and the EAG to conduct this assessment of previously-approved response waning values from dupilumab in AD for the BSC arm. While expert judgement is associated with a likelihood of bias, SEE methodology aims to minimise biases and provide balance to the uncertainty in the absence of empirical evidence. Key limitations in the SEE are as follows: (55)

- Due to the rarity of PN and the objective to select experts with both trial and post-trial experience, only four experts were suitable for recruitment into the study and only three provided quantifiable answers that could be pooled. Thus, there is uncertainty whether the results reflect the full diversity of opinion across relevant dermatology experts treating PN in UK clinical practice.

- The SEE used a bisection approach and only elicited the median value, along with the plausible upper and lower limits. While this method may have made it more difficult to fit

parametric distribution that reflects the experts' judgements, it avoided the risk of overcomplicating the exercise and reducing the quality of the estimates in the interest of minimising respondent fatigue.

- Certain utility values may be unobservable to clinical experts, creating challenges in obtaining reliable results. We therefore elicited reduction in overall HRQoL maintained at different timepoints, rather than absolute utilities.

Despite these limitations, the SEE provided quantitative information on the HRQoL benefits of dupilumab maintained after trial completion in patients with PN, which was otherwise not available. It is noteworthy that all the clinicians, including during the interview conducted prior to undertaking the SEE, agreed that BSC patients would not be able to maintain high levels of response in the real world setting. As the base utility values were already approved from AD, inclusion of these values for the BSC arm in sensitivity analysis is a conservative assumption.(55)

Table 23. Probability of dupilumab plus BSC patients having a sustained response in Years 2-5+ in the PN model using AD data as proxy

Year	Dupilumab plus BSC	
	Base case	Sensitivity analysis
	AD OLE study, %	AD dermatologist survey, %
Year 2	91.4	98.0
Year 3	97.2	96.9
Year 4	90.9	97.9
Years 5+	90.9	98.9
Source	Analysis of long-term efficacy maintenance alongside the OLE study of dupilumab in AD;(2) (see Appendix T for summary of study)	Assumptions based on clinician estimates for the preparation of a CEM of dupilumab in the treatment of AD in TA534(2)

AD = atopic dermatitis; BSC = best supportive care; CEM = cost-effectiveness model; OLE = open-label extension; PN = prurigo nodularis

Table 24. Probability of BSC patients having a sustained response in Years 2-5+ in the PN model

Year	BSC	
	Base case	Sensitivity analysis
	NICE assumption in AD, %	Structured expert elicitation in PN, %
Year 2	75	[redacted]
Year 3	50	[redacted]
Year 4	25	[redacted]
Years 5+	0	[redacted]
Source	Estimates presented by clinicians appointed by NICE(2)	Estimated based on structured expert elicitation in PN(55)

AD = atopic dermatitis; BSC = best supportive care; NICE = National Institute for Health and Care Excellence; PN = prurigo nodularis

B.3.3.2.3 Annual discontinuation rates

The model includes an annual probability of discontinuation input that represents the annual rate at which patients discontinue dupilumab each year due to lack of long-term efficacy, AE, patient preference or clinician preference. The annual probability of discontinuation is applied to patients in the 'Response' treatment state. In the base case, the model uses pooled all-cause drug discontinuation from the PRIME2 and PRIME trials as a proxy for the loss of response over the model time horizon. That is, the discontinuation rate in the trials is used as the transition probability from 'Response' to 'No response'. Clearly BSC patients do not discontinue their treatment. Pooled data of dupilumab in PN from the PRIME2 and PRIME trials were used in the model (Table 25). The annual discontinuation rate for dupilumab taken from the PRIME2 and PRIME trials ([redacted]) is similar to the rate used in the appraisal of dupilumab in AD ([redacted]; TA534).(2) The stopping rate for patients with AD was based on data from the 52-week CHRONOS trial and was further validated in the first 100 weeks of an open-label extension study.(2)

Table 25. Annual discontinuation rates available in the model

Treatment	Annual all-cause discontinuation rate[a]	
	PRIME2 and PRIME trials (base case), %	**CHRONOS trial, %**
Dupilumab	[redacted]	[redacted]
BSC[c]	[redacted]	[redacted]
Source	Sanofi data on file, 2022(55)	NICE TA guidance TA534(2)

BSC = best supportive care; NICE = National Institute for Health and Care Excellence; NR = not reported; TA = technology appraisal.
[a] Annual discontinuation rates were calculated by extrapolating the 24-week clinical trial data on discontinuation rates.
[b] The accepted annual stopping rate used in TA534, for people with moderate to severe AD receiving dupilumab plus TCS as maintenance therapy. This rate was based on the observed probability of Week 16 responders discontinuing treatment by Week 52 in the trial CHRONOS and was supported by data from an open-label extension study.
[c] BSC patients do not discontinue treatment. The movement from 'Response' to 'No response' for these patients must be captured in order to account for the accrual of different utilities and costs.

B.3.3.2.4 Mortality

All-cause mortality is estimated based on National Life Tables for the UK.(95) The model assumes patients do not have an increased risk of mortality due to PN.

B.3.4 Measurement and valuation of health effects

In this section we report the results of the HRQoL SLR, followed by the HRQoL measured in the dupilumab clinical trial programme (PRIME2 and PRIME) which was used in the economic model.

Utility weights are used in the model to calculate the QALYs to reflect the improvement in the HRQoL experienced by patients through the PN clinical trials. The utilities were collected from the PRIME2 and PRIME trials.(53) No suitable utilities were identified in the SLR.

B.3.4.1 Summary of utility data identified in the clinical and economic SLRs

A clinical SLR conducted with a data cut-off of 16th December 2022 identified four RCTs and two non-RCTs assessing the HRQoL of patients with PN. Similarly, an economic SLR conducted with the same data cut-off of 16th December 2022, identified three studies reporting utility data for the pharmacological treatments of PN that are relevant to the economic analyses (of which one was an abstract-only article). Full details of the SLR methodology, study selection process, inclusion and exclusion criteria and results are presented in Appendix H. Overall, none of the HRQoL or utility studies identified in the SLRs reported appropriate information for the model (Table 26).

The DLQI and EQ-5D-5L data collected in the PRIME2 and PRIME trials represent the best available HRQoL and utility data for patients with moderate-to-severe PN whose disease was inadequately controlled with topical prescription therapies. Therefore, the trial-based utilities are used to inform the economic model.

Table 26. HRQoL and utility studies identified in the clinical and economic SLRs

Reference	Description of available data	Reason for exclusion from the economic model
Studies reporting HRQoL		
Ständer, 2020(96)	DLQI in patients with PN (IGA PN-S moderate and severe; N=70) Phase 2 RCT, Austria, France, Germany, Poland, US	The study only reported mean change in DLQI and proportion of patients with improvement, which are not aligned with input requirements for the model.
Siepmann, 2013(97)	DLQI in patients with PN (VAS >3; N=30) Phase 2 RCT, Germany	The study is limited to 30 patients. DLQI was only reported for the entire patient population, which does not provide inputs aligned with the multiple health states in the economic model.
Tsianakas, 2019(98)	DLQI, ItchyQoL and HADS in patients with PN (mean baseline VAS ≥7; N=58) Phase 2 RCT, Germany	The study only reported time course changes in DLQI, ItchyQoL and HADS, which are not aligned with input requirements for the model.
Weisshaar, 2022(99)	ItchyQoL and HADS in patients with moderate-to-severe PN (N=63) Phase 2 RCT, North America, Europe	The study only reported reduction from baseline in ItchyQoL and HADS, which are not aligned with input requirements for the model.
Chiricozzi, 2019(100)	DLQI in patients with PN (IGA PN-S 4 or 5; N=27) Retrospective study, Italy	The study is limited to 27 patients and DLQI was only reported for the entire patient population, which does not provide inputs aligned with the multiple health states in the economic model.
Napolitano, 2020(101)	DLQI in patients with PN (N=9) Retrospective study, Italy	The study is limited to nine patients with PN and does not report disease severity, so the study population may not be equivalent to the population in the submission

Reference	Description of available data	Reason for exclusion from the economic model
Studies reporting utilities		
Whang, 2022(83)	HUI3 values in patients with PN (N=36) Cohort study, US	HUI3 is not the preferred utility, with NICE preferring EQ-5D utility measures. The study is limited to 36 patients with PN and does not report disease severity, so the study population may not be equivalent to the population in the submission
Whang, 2020(102)	HUI3 values in patients with chronic pruritus (N=95) Cross-sectional survey, US	HUI3 is not the preferred utility, with NICE preferring EQ-5D utility measures. This study was available as an abstract only, which reported no specific PN utilities (only total QALYs from a cost-effectiveness model that was not described in detail)
Todberg, 2020(16)	VAS and DLQI in patients with PN (N=52) Cross-sectional survey, Denmark	The study did not report the required parameters to allow mapping of DLQI outcomes to EQ-5D (e.g., age, gender, DLQI sub-item scores). The study only reported mean DLQI for patients with PN, which is not sufficient for the model.

DLQI = Dermatology Life Quality Index; EQ-5D = EuroQoL five-dimension; HADS = Hospital Anxiety and Depression Scale; HRQoL = health-related quality of life; HUI3 = Health Utilities Index Mark 3; IGA PN-S = Investigator's Global Assessment 0 or 1 score for Prurigo Nodularis – Stage; NICE = National Institute for Health and Care Excellence; PN = prurigo nodularis; QALY = quality-adjusted life year; RCT = randomised controlled trial; SLR = systematic literature review; US = United States; VAS = visual analog scale.

B.3.4.2 Health-related quality-of-life data from clinical trials used in the model

The base case cost-effectiveness analysis incorporates utility data from the clinical trial programme (PRIME2 and PRIME trials) collected using the EQ-5D-5L instrument and valued using the UK tariff (Table 27). This is the most appropriate source of data since it is derived directly from patients with the condition and, in the group of patients forming the base case, baseline characteristics and treatment history are consistent with the patients for whom use in the NHS is expected. Utility data in the trials were collected at specific timepoints (baseline, Week 12, Week 24).

Table 27. EQ-5D single index score in the pooled ITT population

	EQ-5D-5L from PRIME2 and PRIME trials.(67)		**Conversion to EQ-5D-3L with UK crosswalk tariffs (Hernández Alava 2020; base case).(91)**		**Conversion to EQ-5D-3L with UK crosswalk tariffs (van Hout 2012; sensitivity analysis).(91, 103)**	
	BSC	**Dupilumab**	**BSC**	**Dupilumab**	**BSC**	**Dupilumab**
Baseline	**N=156**	**N=153**	**N=156**	**N=153**	**N=156**	**N=153**
Mean (SD)	0.640 (0.258)	0.621 (0.261)	0.662 (0.257)	0.643 (0.262)	0.640 (0.258)	0.621 (0.261)
Median	0.725	0.725	0.722	0.723	0.725	0.725
Week 12	**N=153**	**N=152**	**N=153**	**N=152**	**N=153**	**N=152**
Mean (SD)	0.72 (0.20)	0.76 (0.22)	0.735 (0.206)	0.766 (0.214)	0.724 (0.204)	0.758 (0.215)
Median	0.77	0.79	0.762	0.791	0.767	0.787
Week 24	**N=145**	**N=152**	**N=145**	**N=152**	**N=145**	**N=152**
Mean (SD)	0.72 (0.22)	0.76 (0.22)	0.729 (0.218)	0.779 (0.218)	0.721 (0.221)	0.765 (0.220)
Median	0.77	0.80	0.784	0.817	0.768	0.796

BSC = best supportive care; EQ-5D-3L = Euroqol 5-dimension 3-level; EQ-5D-5L = Euroqol 5-dimension 5-level; ITT = intent-to-treat; SD = standard deviation; UK = United Kingdom

The utilities collected in the PRIME2 and PRIME trials used the EQ-5D-5L questionnaire.(53) For use in this analysis and in accordance with NICE's latest guidelines (2022), these utilities were converted to the three-level EQ-5D (EQ-5D-3L) using crosswalk algorithms.(89) The following two such algorithms were used: the algorithm by Hernández Alava (base case) and the algorithm by van Hout (sensitivity analysis).(91, 103) The former is NICE's preferred option and so is used as the base case while the latter is used in sensitivity analysis.(89)

The utilities used in the model were derived from the PRIME2 and PRIME clinical trials.(53) A multiple linear regression approach was used to derive these. This was based on least squares mean change for the calculation of follow-up, with the same model as above.

The base case used the approach where utilities derived by a linear regression using the algorithm by Hernández Alava (2020).(91) This choice was motivated by advice from health economics experts received during the global advisory board in April 2022.(63) The experts indicated that regression equations are the most suitable for obtaining utilities among the approaches presented to them.(63)

B.3.4.2.1 Mixed-model regressions used to calculate utilities

For the base-case analysis, the utility weights were estimated using a mixed-model regression based on the data collected in the PRIME2 and PRIME trials. The analyses were performed using SAS version 9.4 (Cary, NC: SAS Institute; 2012). Linear mixed models were fitted to the EQ-5D-5L utility score as the response variable using a forward selection process after controlling for age, gender, baseline EQ-5D utility score and baseline DLQI score in each trial with the following variables as predictors:

- DLQI score (reported at Weeks 12 and 24 in the trials)
- WI-NRS score (reported at Weeks 12 and 24 in the trials)

The model coefficients and diagnostic plots are shown in Table 28, Figure 16 and Figure 17. Please refer to Appendix S for the covariance matrices.

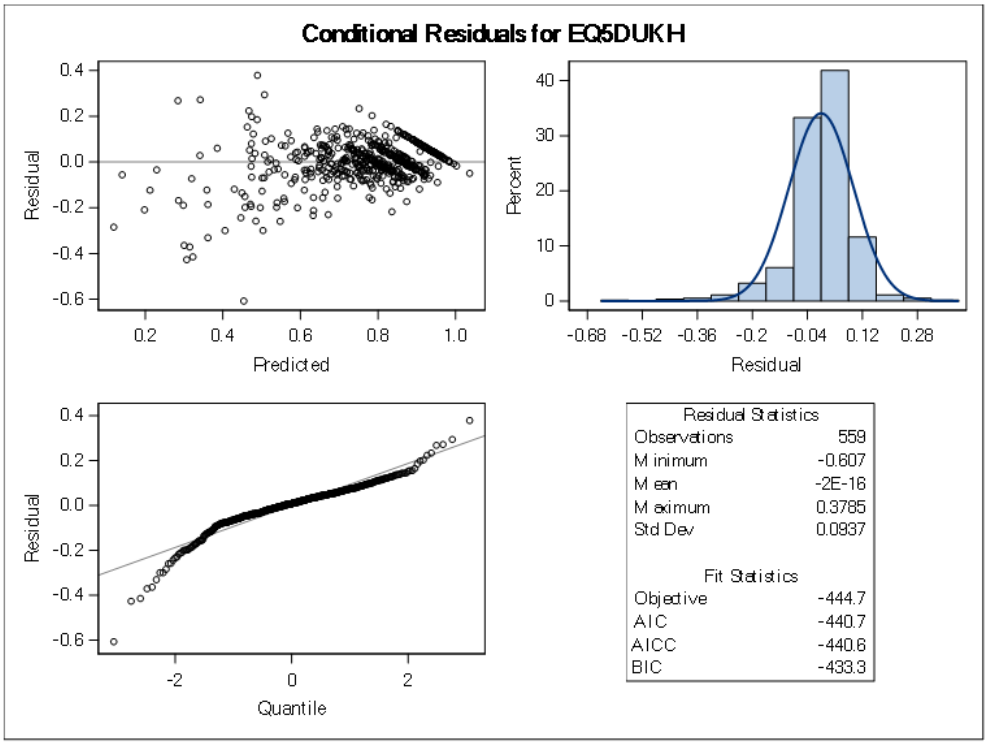
Table 28. Model coefficients

Covariates	Algorithm by Hernández Alava (2020) (Base case)(91)		Algorithm by van Hout (2012) (Sensitivity analysis)(103)	
	Coefficient	*P* value	Coefficient	*P* value
Intercept	0.5892	<0.0001	0.6425	<0.0001
Age at baseline	-0.0009	0.0955	-0.0008	0.122
Gender = male	0.0352	0.0526	0.0342	0.0646

Covariates	Algorithm by Hernández Alava (2020) (Base case)(91)		Algorithm by van Hout (2012) (Sensitivity analysis)(103)	
	Coefficient	*P* value	Coefficient	*P* value
Baseline EQ-5D-5L utility weight	0.3624	<0.0001	0.3034	<0.0001
Baseline DLQI score	0.0055	0.0002	0.0049	0.0012
DLQI score at follow-up[a]	-0.0109	<0.0001	-0.0114	<0.0001
WI-NRS score at follow-up[a]	-0.0062	0.0723	-0.0076	0.0347

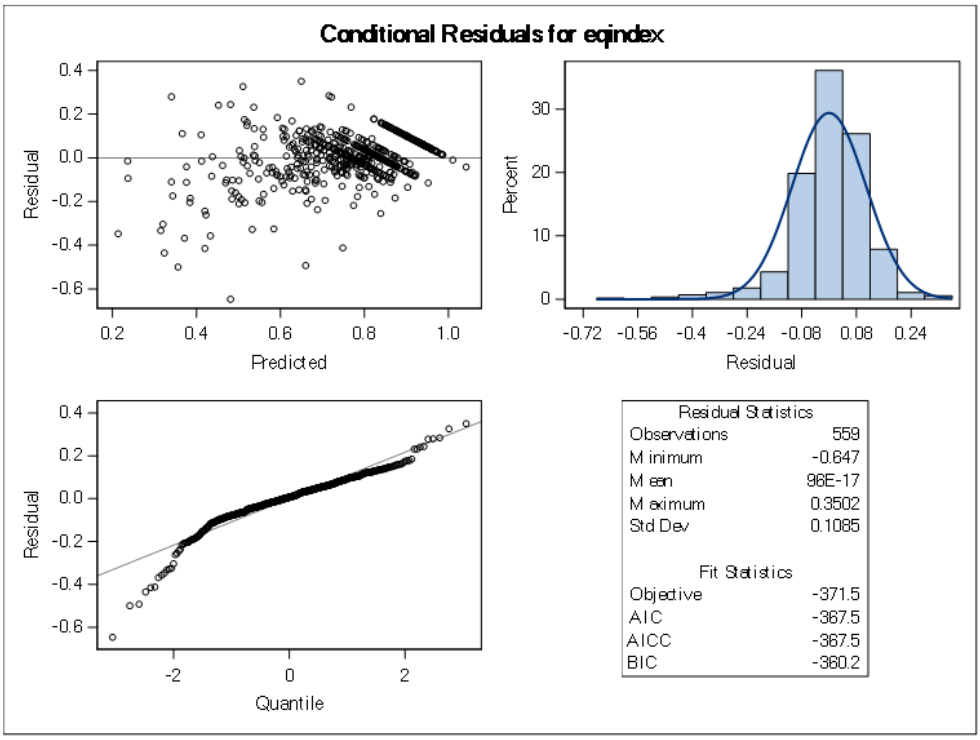
DLQI = Dermatology Life Quality Index; EQ-5D-5L = Euroqol 5-dimension 5-level; WI-NRS = worst-itch numerical rating scale.
[a]Current score = baseline score + least squares change from baseline.

Figure 16. Mixed-model diagnostics: algorithm by Hernández Alava (2020)



AIC = Akaike information criterion; AICC = Akaike information criterion corrected for sample size; BIC = Bayesian information criterion; EQ5DUKH = regression model using algorithm by Hernández Alava (2020).

Figure 17. Mixed-model diagnostics: algorithm by van Hout (2012)



AIC = Akaike information criterion; AICC = Akaike information criterion corrected for sample size; BIC = Bayesian information criterion; Equindex = regression model using algorithm by Hout et al. (2012).

Table 29 presents the comprehensive set of utility weights available in the analysis derived using the methods described above. As previously mentioned, the utilities used in the model were all derived from the PRIME2 and PRIME clinical trials.

Table 29. All utility weights available in the analysis(53, 91, 103)

Method used to derive utilities	Algorithm used	Baseline	Pooled response		Separate response			
			Week 12		Week 24			
					Responders		Non-responders	
		Pooled arms[a]	Dupilumab	BSC	Dupilumab	BSC	Dupilumab	BSC
Regression based on LS mean	Hernández Alava	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Van Hout	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC = best supportive care; LS = least squares
[a]For pooled arms, the utilities were calculated using a weighted average of each arm

The base case used the utilities derived via multiple linear regression, based on least squares mean change from baseline for the calculation of follow-up, and with the algorithm by Hernández Alava (2020).(91) These utilities are listed in Table 29 from which the working utilities for the model base case had to be chosen. The sets of utility values selected for the

base case for the decision tree and Markov model are presented in Table 30 and Table 31, respectively.

B.3.4.3 Implementation of utility data in the model

Utility accrual in the decision tree portion of the model (Table 30) is implemented from baseline to Week 12 and Week 12 to Week 24. From baseline to Week 12, utilities are assumed to be the same across treatment arms based on the pooled baseline value in the clinical trials. From Week 12 to Week 24, utilities are assumed to vary by treatment arm based on the utility values observed in the clinical trial over this time period. At Week 24, patients are assessed for response status and enter the Markov portion of the model based on response status and treatment arm.

In the Markov portion of the model (Table 31), utility is accrued based on response status and treatment arm. Utility values are drawn from the PRIME2 and PRIME clinical trials at Week 24 by treatment arm and response status. Utility differs between arms for responders and non-responders because a treatment-based approach is taken; patients treated with dupilumab generally have a higher utility than those with BSC after 12 weeks (although this benefit may appear before 12 weeks due to the fast resolution of itch with dupilumab). However, as data are unavailable to support this, a conservative assumption for utility weights across treatment arms and response status has been used.

Table 30. Utility weights used in the base case of the decision tree

Time period	Dupilumab arm	BSC arm	Rationale
Baseline to Week 12			Patients were well-matched in the clinical trial. The same baseline value applies to both arms
Utility value	[redacted]	[redacted]	
Assumed same as	Baseline		
Week 12 to Week 24			These utility values are as observed in the clinical trial over this time period
Utility value	[redacted]	[redacted]	
Assumed same as	Dupilumab patients at Week 12	BSC patients at Week 12	

BSC = best supportive care

Table 31. Utility weights used in the base case of the Markov portion

Treatment response state	Dupilumab arm	BSC arm	Rationale
Responder			Observed utility varies by treatment arm and response as observed at Week 24 of the clinical trial.
Utility value	[redacted]	[redacted]	
Assumed same as	Dupilumab responders at Week 24	BSC responders at Week 24	
Non-responder			
Utility value	[redacted]	[redacted]	
Assumed same as	Dupilumab non-responders at Week 24	BSC non-responders at Week 24	

BSC = best supportive care

B.3.4.4 Change in HRQoL over time

No extension studies have been conducted in PN to provide data on the real-world effectiveness of dupilumab or BSC in PN following the PRIME2 and PRIME trials. Thus, the probability of sustained response (and maintenance of HRQoL) was extrapolated for the PN model. Please refer to Section B.3.3.2.2 where our approach has been previously described.

To summarise, we considered the a priori approach to defining the decline in HRQoL based on the committee-preferred assumptions in previous NICE appraisals in AD. To investigate response waning in PN specifically, including protocol-driven effect in the BSC arm, we conducted a clinician interview and subsequently a SEE. Using these data as a starting point, we adapted the assumptions to provide a set of inputs for the base case and scenario analysis in the PN model. Please see Table 23 and Table 24 where the final response waning values used in the PN model have been previously tabulated.

B.3.4.5 Utility adjustments based on age

The utility regression equation contains a covariate that adjusts for age. Furthermore, age adjustments were made over time using the multiplicative method applying the general population utility weights from Ara and Brazier (2017) to estimate the relative decline over time.(104)

B.3.4.6 Mapping

Mapping was not carried out as the data were collected directly from relevant clinical studies.

B.3.4.7 Adverse reactions

Disutilities due to AEs are not included in the model. AEs arising from treatment during the trial programme were generally mild and transient (Section B.2.10). Therefore, it is not expected that there would be a significant decrement to HRQoL associated with these events. Furthermore, the frequency of utility collection in the clinical trials is sufficient to capture any potential decrements related to AEs.

B.3.5 Cost and HCRU identification, measurement and valuation

A number of activities were undertaken to identify resource utilisation rates and unit costs most appropriate to this submission:

- A systematic review of the literature to identify published and unpublished studies.
- A retrospective cohort BOI study to understand the HCRU of patients with moderate to severe PN.

- Advisory board conducted in December 2022 to validate UK clinicians' perceptions on HCRU among their PN patients.

B.3.5.1 Systematic review of the literature to identify published and unpublished studies

An economic SLR conducted with a data cut-off of 16th December 2022 identified 13 studies reporting costs and HCRU, which were conducted in multiple European locations (including Denmark and Germany) and the US. The review did not identify any studies reporting costs and HCRU in England or the UK (Table 32). Full details of the economic SLR methodology, study selection process, inclusion and exclusion criteria and results are presented in Appendix I.

Table 32. Cost and HCRU studies identified in the economic SLR

Reference	Description of available data	Reason for exclusion from the economic model
Pereira, 2021(23)	Out-of-pocket costs and drug utilisation for 406 patients with CNPG (N=406) Cost-year NR, Euros, Germany and Northern, Central, Eastern and Southern Europe	Choosing the right currency conversion rate is difficult because the cost-year is not reported. Additionally, the mean out-of-pocket cost per patient is not presented by region.
Wongvibulsin, 2021(105)	Health care utilisation of specialty care by the patients and number of visits per year per patient using data from patients with PN in 2016 (N=2,658) Claims data from 2015-2019, currency NR, US	The data are for the US and would not be suitable for a UK model.
Aggarwal, 2021(43)	Health care resource utilisation for patients with PN (N=171) Cost-year and currency NA, US	The data are for the US and would not be suitable for a UK model.
Sutatria, 2021(106)	Cost of care, LOS, hospitalisations, available for infectious disease hospitalisations where the patient had PN (N=3,040) Cost-year NR, US dollars, US	Costs are limited to infectious disease admission for patients with PN, which is not examined in the submission model. The data are for the US and would not be suitable for a UK model.
Nguyen, 2020(107)	Drug utilisation, health care utilisation for PN ambulatory visits, from 2007 to 2016 (estimated N=1.5 million) Cost-year and currency NA, US	The presentation of the data is not useful, as it is not PPPY or per month. The data are from the US and thus would not be suitable for a UK model.
Huang, 2020(108)	Health care utilisation for patients with PN (N=7,095) Currency year not reported, US dollars, US	Total health care spending per patient was over a 15-month period rather than a 12-month period. The data are from the US and thus would not be suitable for a UK model.
Whang, 2020(102)	Lifetime financial burden of patients who are Black and have PN compared with patients who are White and have PN (N=95) Cost-year NR, US dollars, US	The model is not a lifetime model and the abstract provides no details on how the QALY loss translates to financial burden. The data are from the US and thus would not be suitable for a UK model.
Todberg, 2020(16)	Drug utilisation and productivity loss patients with PN (N=52) Cost-year and currency NA, Denmark	Data are not presented as PPPY or per month.

Reference	Description of available data	Reason for exclusion from the economic model
Whang, 2019(109)	Hospitalisations, cost of care and LOS for patients with PN who were discharged from hospital in 2016 (N=265) Cost-year was not explicitly stated, but assumed 2016 US dollars, US	The study population may not be comparable to the model population since age and sex are not reported. The data are from the US and thus would not be suitable for a UK model.
Han, 2022(110)	Mental Health Service Utilisation according to socio-economic status Cost-year and currency NA, US	Data is not presented per patient, per period. The data are from the US and thus would not be suitable for a UK model.
Ständer, 2022(111)	Drug utilisation and costs, resource use for related specialist visits among patients with PN (N=4,204) 2010, Euros, Germany	The data are from Germany and thus would not be suitable for a UK model.
Le, 2022(112)	Cost of care and LOS available for patients diagnosed with PN and discharged from the hospital (N=3,040) Cost-year NR, US dollars, US	Results are focused on patients with PN and comorbid mental health disorder. The data are from the US and thus would not be suitable for a UK model.
Adawi, 2022(113)	Cost of care and LOS for patients diagnosed with PN and with hospitalisations for comorbid GI and hepatobiliary diseases (N=4,815) Cost-year NR, US dollars, US	Results are focused on patients with PN and comorbid GI or hepatobiliary disease. The data are from the US and thus would not be suitable for a UK model.

CNPG = chronic prurigo of nodular type; GI = gastrointestinal; HCRU = healthcare resource use; LOS = length of stay; NA = not applicable; NR = not reported; PN = prurigo nodularis; PPPY = per patient per year; QALY = quality-adjusted life-year; SLR = systematic literature review; UK = United Kingdom; US = United States.

Overall, this SLR demonstrated that there is little evidence upon which to base HCRU estimates relevant to UK clinical practice today. Given the paucity of information in the literature, we have based our estimates for resource use implemented in the economic modelling on the sources below (Section B.3.5.4). Justification for the choice of the base case estimates is provided in Section B.3.5.2 and Section HCRU = healthcare resource use; PN = prurigo nodularis.

B.3.5.3.

B.3.5.2 Retrospective BOI study in England

A non-interventional retrospective cohort study was conducted to evaluate the prevalence and incidence, patient characteristics and healthcare resource utilisation associated with PN in England.(35)

Results from this study were presented at ISPOR EU 2022 and will be published in a manuscript later in 2023.(36) For more detailed information on the study results see Appendix N.

B.3.5.2.1 Study design and setting

Patient data were derived from the CPRD GOLD and Aurum primary care datasets linked to HES.(35) The patient follow-up period ranged from the beginning to end of the patient record, with historical data (prior to the patient record data used in the study) for chronic previous comorbidities.(35) The enrolment period was between 1st April 2007 to 1st March 2019.(35)

B.3.5.2.2 Patient population

Suitable patients were selected in the first instance if they had ≥1 record of a medical or International Classification of Diseases 10th Revision code indicative of PN.(35) Patients were selected if their index date fell within the enrolment period and were required to have ≥12 months follow-up from their index date to the end of their patients record (excluding those that died).(35) Three patient populations were considered in the study:(35)

- The PN cohort whose index date was defined as the first ever record of a PN diagnosis.
- The moderate-to-severe PN cohort whose index date was defined as the first ever record of a prescription for systemic immunosuppressants or gabapentinoids with a prior PN diagnosis.
- The mild PN cohort defined as any patient with a PN code in either primary or secondary care that never received a prescription for systemic immunosuppressants or gabapentinoids.
- To understand the incremental cost associated with moderate-to-severe PN, patients with moderate-to-severe PN were directly matched 1:1 (for age and gender) to patients with mild PN. The index date of patients with mild PN were set to the corresponding index date of the patients with moderate-to-severe PN.

B.3.5.2.3 Results

Results for prevalence, incidence and patient characteristics have been presented earlier in the submission (Section B.1.3.1).

A summary of the rates of HCRU per patient year (PPY) during all follow-up for the matched cohort of patients with mild and moderate-to-severe PN is presented in Table 33.(35) Primary care visits were significantly higher in patients with moderate-to-severe PN (21.27 PPY) compared to patients with mild PN (11.35 PP; p<0.001).(35) Hospitalisation rates (inpatient dermatology visits) during the all follow-up period remained low, but were significantly (p<0.001) higher in patients with moderate-to-severe PN (0.004 PPY) compared to patients with mild PN (0.01 PPY).(35)

Similar trends in HCRU were reported in the sensitivity analysis, in which patients were matched for comorbidities as well as age and gender.(35)

It is important to note these results may not represent the true resource use of patients with PN due to challenges in clinical management which make it difficult to assess the full healthcare burden of PN. Clinicians who participated in the global advisory board in April 2022 and in the UK advisory board conducted by Sanofi in December 2022 (Section B.3.5.3 Advisory board to evaluate UK clinicians' perceptions of healthcare resource use) highlighted that patients are commonly under-referred for PN, driven by difficulties in proper diagnosis and lack of precise codes for PN.(1, 63)

Table 33. HCRU in England (rates per patient year) – age and gender matched cohort(35)

Resource	Mild PN	Moderate-to-severe PN
Primary care visit	11.35	21.27
Outpatient visit (any speciality)	4.87	10.72
Emergency room visit	0.44	0.95
Inpatient hospitalisation (dermatology)	0.01	0.04
Inpatient hospitalisation (PN specific primary)	0.01	0.02
Inpatient day case	0.26	0.57

HCRU = healthcare resource use; PN = prurigo nodularis.

B.3.5.3 Advisory board to evaluate UK clinicians' perceptions of healthcare resource use

Sanofi organised an advisory board in December 2022 to discuss the HCRU of PN patients with moderate-to-severe disease who may be candidates for dupilumab. The advisory board included two UK clinicians and one health economics and outcomes research expert who assessed resource use for responders and non-responders in terms of consultant dermatology visits, general practitioner visits, accident & emergency visits and hospital in-patient stays. The clinicians were asked to consider the resource use values from the retrospective BOI study conducted in England, as well as those from TA534 (Section B.3.1.3) that were accepted by NICE for AD. Table 34 presents the proposed HCRU values from the clinicians alongside their comments.

The clinicians noted that patients with PN are highly symptomatic and require long-term, frequent follow-up. Despite this need for management, patients are frequently under-referred for PN and it is challenging for dermatologists to properly diagnose patients with PN, and harder still for general practitioners. Patients who do not respond to treatments have more visits to healthcare professionals than responders. These non-responders are moved between hospitals and departments, and can get 'lost' in the healthcare system. Thus, some

of the HCRU of patients with PN may be accounted for under the primary care category, instead of under dermatologist outpatient visit. Further, amongst these outpatient visits, coding for dermatology may not be performed accurately. Clinicians noted that ideally they would like to see patients more at rates similar to pre-COVID-19 pandemic setting.(1)

Additional input was considered from clinicians in a global advisory board conducted by Sanofi in April 2022. It was noted that identifying resource use via PN disease coding uses many assumptions as there are no precise codes for PN. For example, it would likely be difficult to accurately identify patients with PN from an analysis of general practitioner databases using disease coding.(63)

In terms of other costs, the clinicians suggested to include cosmetics, psychologists, phototherapy and alternative medicines which are commonly used in patients with PN, such as acupuncture, homeopathy, nutrition, cannabidiol, meditation and phytotherapy. Some patients also undergo patch-testing for contact allergens. Note that our model does not consider all of these costs, thus our estimates are likely to be conservative.(63)

Table 34. Proposed annual HCRU values from UK clinicians in December 2022 advisory board

	Resource use frequency PPPY		Clinician comments
	Responder	Non-responder	
Primary care visit	2.0	6.0	Experts assumed two and six physical (in-person) visits between the groups, respectively. However, they emphasised that most of the time patients would be dealt with via e-consultation and the number of visits including these e-consults can be around 10-12 per patient per year
Dermatologist outpatient visit	2.0	4.0	The experts allocated two visits for responders (first visit + follow-up) and at least double for non-responders. Clinicians recognise the capacity issues for most patients, but they would routinely see highly symptomatic patients more frequently (i.e., patients with highest burden) under normal NHS conditions Experts said they would see these patients four to six times per year. The consensus was four visits but higher values could be tested
Dermatology nurse visit	1.0	2.0	Experts allocated one and two visits between the groups, respectively
Emergency room visit	0.0	0.0	Experts do not expect to see patients regularly in this setting
Hospitalisation (inpatient; dermatology)	0.01	0.04	Experts expect to see patients in inpatient care rarely and therefore the healthcare burden study inpatient dermatology results using the CPRD data is correct to describe inpatient dermatology visits. Under normal NHS conditions, values from TA534 would be realistic(2)

Day case	0.000	0.075	Experts expect to see non-responders in 5/100 to 10/100 per year (i.e., 0.05 to 0.10) but they wouldn't expect to see patients on dupilumab (defined as responders in the model); considering easy access to day care

CPRD = Clinical Practice Research Datalink; HCRU = healthcare resource use; NHS = National Health Service; PPPY = per patient per year; UK = United Kingdom

B.3.5.4 Choice of resource use data by response status

HCRU inputs in the cost-effectiveness model define the annual number of resource units used in each model arm. Unit costs are applied to the number of each resource use category calculated by the model to estimate the total annual HCRU costs for each arm. See Section B.3.5.6.2 below for an explanation of the costs used.

To ensure the pharmacoeconomic analysis was based on the most credible set of inputs, we synthesised all available sources of data. Table 35 presents the final resource use data implemented in the base case for responders and non-responders alongside our rationale. Data were applied based on feedback from clinicians (who attended the UK advisory board; December 2022; Section B.3.5.3 Advisory board to evaluate UK clinicians' perceptions of healthcare resource use) on the BOI study results (Section B.3.5.2) and the NICE appraisal for dupilumab in AD (TA534; Section B.3.1.3). We consider clinicians to be the most appropriate data source since they have extensive knowledge and long-term experience managing patients with PN in UK clinical practice. However, as PN is a rare disease, clinical experts acknowledge that there is some uncertainty around estimates.(1)

The resource use value for primary care visits was set to 11 per patient per year (PPPY) for non-responders, based on clinician input during the advisory board.(1) This is a conservative estimate compared with 21.27 PPPY primary care visits for patients with moderate-to-severe PN observed in the BOI study. We recognise this is a very high number and consequently the data was scrutinised in depth to ensure it was accurate. All of the visits were coded appropriately and consisted of a mixture of face-to-face GP appointments, practice nurse visits and telephone consultations.(35) This finding further highlights the significant healthcare capacity burden due to PN in primary care.

For dermatology outpatient visits, resource use values were chosen to be the central estimate from the range provided by clinicians in the advisory board (five out of a range of four to six PPPY for non-responders).(1) Similarly, this is low compared with 11.27 PPPY for outpatient visits (any speciality) for moderate-to-severe PN observed in the BOI study.(35) This value may be more representative of the healthcare resource burden because clinicians noted that labelling and tracking patients with PN is a challenge, due to issues with disease

coding and patients being moved between hospital departments. Thus, these 'lost' patients may be reflected in the outpatient visit (any speciality) value from the BOI study. However, we have chosen the clinician estimate for the base case to align more closely to the previously accepted value for AD and to ensure that the model takes a conservative approach.

Hospitalisation is a rare event for PN patients in contrast to AD patients, thus estimates of hospitalisation used in the model were assigned based on data from the BOI study rather than those from the previous AD submission. Hospitalisation estimates from the BOI study were lower than those from the previous AD submission and were validated by clinicians.(1, 35) Data from the BOI study include:(35)

- Responders: values based on data from patients with mild PN in the BOI study (0.01 PPPY).
- Non-responders: values based on patients with moderate-to-severe PN in the BOI study (0.04 PPPY).

Other HCRU values were based on the precedent provided by the dupilumab in AD appraisal (TA534), including day case, full blood count, background medication (including emollients), phototherapy and psychologist visit. AD is an analogous disease to PN with comparable impact on HRQoL (Section B.3.1.3). Clinicians noted the high disease burden in patients with PN, highlighting comparable, if not greater, burden to AD. This insight is consistent with previous published comparisons of AD and PN patients.(86) Use of these HCRU values from AD were applied based on extensive discussions with multiple clinicians to validate their use in the PN setting.

Clinicians commented that in the post-COVID-19 pandemic setting, where pressure on healthcare capacity has substantially increased, it is likely that less time will be spent with patients. They recognised that the resource use estimates accepted for AD may be higher than the capacity available to treat PN patients in the current climate. Thus, our assumptions for HCRU implemented in the PN model are conservative.

HCRU values from previous NICE appraisals in AD are further explored in sensitivity analysis, including TA534 (Table 36) and TA814 (Table 37).

Table 35. HCRU values for PN model

	Resource use frequency per patient year		Source and justification
	Responder	Non-responder	
Primary care visit	2.00	11.00	UK advisory board (December 2022);(1) Note these values are conservative as they are lower than in the retrospective BOI study in England (mild PN: 11.35; moderate-to-severe PN: 21.27).(35) Mid-point between clinician estimates (Table 34) and the BOI study. Clinicians stated consultations could be 10–12 per year based on additional remote consultations.
Dermatologist outpatient visit	2.00	5.00	Synthesis of best available evidence including UK advisory board (December 2022)(1) plus the supportive retrospective BOI study in England (taking into account the value for 'outpatient visit (any speciality)' and accounting for challenges with proper patient diagnosis and coding; Table 33).(35) Based on clinician input that the number is likely between four to six visits per year, five visits has been chosen as the mid-point in this range.(1) One clinician said they would like to see symptomatic patients more often than four times per year if capacity allowed.(1)
Dermatology nurse visit	1.00	2.00	UK advisory board (December 2022)(1)
Hospitalisation (inpatient; dermatology)	0.01	0.04	BOI study (Section B.3.5.2).(35) Age- and gender-adjusted values (from mild PN patients for responders and moderate-to-severe PN for non-responders); no change from PN UK advisory board (December 2022)
Day case	0.00	0.17	TA534.(2) Values based on secondary care case note review to characterise resource use in AD patients uncontrolled by current therapy(December 2022)(1)
Full blood count	0.00	3.00	TA534.(2) Values based on monitoring costs for systemic treatments in AD patients
Background medication	1.00	2.38	TA534.(2) Clinical opinion solicited for the appraisal in the related dermatological disease of AD suggested that wash products as well as emollients should be considered in the economic modelling.
Phototherapy	1.00	1.20	TA534.(2) Included based on clinician feedback in PN global advisory board (April 2022) to include phototherapy costs.(63)
Psychologist	0	0.1	Assumption. Included based on clinician feedback in PN global advisory board (April 2022) to include psychologists in multidisciplinary teams to address the behavioural aspects of PN.(63)

AD = atopic dermatitis; BOI = burden of illness; HCRU = healthcare resource use; PN = prurigo nodularis; UK = United Kingdom

Table 36. HCRU values from TA534 in the sensitivity analysis of the PN model (annualised)(114)

Resource	Committee preferred values from TA534,

	Responders	Non-responders
Primary care visit	2	12.81
Outpatient visit (dermatologist)	2[a]	7.03
Emergency room visit	0.06	0.25
Inpatient visit (dermatology)	0.03	0.23
Day case	0.00	0.17

HCRU = healthcare resource use; PN = prurigo nodularis
[a]Value for dupilumab responders at Years 2+. Expert opinion stated that dupilumab patients would be seen every three months for the first year and if well-controlled, every six months thereafter.
Source: Sanofi assumptions validated by UK clinicians and a clinician case note review of resource use of patients with AD.

Table 37. HCRU values from TA814 in the sensitivity analysis of the PN model(88)

Visit/test	Number per annum			Number per week		
	Non-responders (BSC)	Responders (MAB)	Responders (BSC/JAKi)	Non-responders (BSC)	Responders (MAB)	Responders (BSC/JAKi)
Dermatologist outpatient consultation	6.000	4.320	4.320	0.115	0.083	0.083
Dermatologist nurse visit	0.460	0.350	0.350	0.009	0.007	0.007
GP consultation	12.810	6.150	6.150	0.246	0.118	0.118
A&E visit	0.082	0.021	0.021	0.002	0.000	0.000
Hospitalisation	0.130	0.017	0.017	0.002	0.000	0.000
Day case	0.200	0	0	0.004	0	0

A&E = accident and emergency; BSC = best supportive care; GP = general practitioner; HCRU = healthcare resource use; JAKi = Janus Kinase inhibitor; MAB = monoclonal antibody; PN = prurigo nodularis

B.3.5.6 Intervention and comparators' costs and resource use

B.3.5.6.1 Drug unit and administration costs

The dosing of dupilumab in PN is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week by subcutaneous injection. The annual cost for dupilumab considering the list price is £16,500 PPPY. [redacted]. In the model, the unit cost per dose was multiplied by the treatment frequency to estimate the cycle-specific drug costs. Table 38 presents the drug acquisition costs for the first year and subsequent years with dupilumab use.

Table 38. Dupilumab drug-acquisition costs

Year	Dupilumab 300 mg drug-acquisition costs
Year 1	[redacted]
Year 2+	[redacted]

Costs included in the BSC arm in the model, which was defined as a combination of emollients, low-to-medium potency TCS/TCI and rescue therapy, are presented in Section B.3.5.6.1.1, Section B.3.5.6.1.2 and Appendix K.

Based on clinical practice for AD, it is assumed that dupilumab patients receive subcutaneous self-injection training once by a hospital nurse and self-administer thereafter. Training is assumed to take one hour of nurse time and cost £55.(115)

B.3.5.6.1.1 TCS/TCI costs

The average acquisition costs of TCS and TCI were estimated based on the British National Formulary and are tabulated below in Table 39 and Table 40.(116-120) TCS costs in the model, assume an average cost across all preparations. This assumption is based on all preparations being used in equal proportions. TCI cost is based on the use of tacrolimus. The TCS and TCI treatment frequencies were estimated based on the assumptions presented in Table 41.

Table 39. Average acquisition costs of TCS and TCIs(116-120)

	Pack size (g)	Acquisition cost per pack, £	Acquisition cost of a 100g pack, £
Mild TCS			
Hydrocortisone 0.1%, cream	15	2.83	18.87
Hydrocortisone 0.5%, cream	30	3.44	11.47
Hydrocortisone 1%, cream	50	4.00	8.00
Hydrocortisone 2.5%, ointment	30	88.00	293.33
Hydrocortisone 1%, ointment	50	8.14	16.28
Moderate TCS			
Betamethasone val. 0.025%, cream	100	3.15	3.15
Betamethasone val. 0.025%, ointment	100	3.15	3.15
Clobetasone but. 0.05%, cream	100	5.44	5.44
Clobetasone but. 0.05%, ointment	100	5.44	5.44
Fluocinolone acet. 0.00625%, cream	50	4.84	9.68
Fluocinolone acet. 0.00625%, ointment	50	4.84	9.68
TCI			
Tacrolimus 0.03%, ointment	60	42.55	70.92
Tacrolimus 0.1%, ointment	60	32.66	54.433

acet. = acetonide ; but. = butyrate; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids; val. = valerate

Table 40. Average acquisition costs of TCS and TCIs(116-119)

	Number of 100 g packs per 12-week cycle	Average acquisition costs per 100 g pack	Acquisition costs per 12-week cycle, £
Mild/Moderate TCS	6.00	34.95	209.72
TCI	2.00	62.68	125.35

TCI = topical calcineurin inhibitors; TCS = topical corticosteroids

Table 41. Assumed TCS and TCI treatment frequencies

	Treatment frequency	Assumption
TCS	100 g every two weeks	It is assumed that for long-term use, topical corticosteroids are used for a variety of skin conditions, applied thinly once a day. According to the BNF, for a once daily application, the following quantities of topical corticosteroids will last for two weeks of treatment: • application to the arms, 30 g to 60 g • application to the legs, 100 g • application to the trunk, 100 g In the PRIME2 and PRIME clinical trials, inclusion criterion number 3 required at least 20 PN lesions in total on both legs, both arms and/or trunk at screening and on Day 1. Therefore, we assume that patients use 100 g of topical glucocorticoid preparation every two weeks.
TCI	100 g every six weeks	The following is assumed: • long-term use of topical medications • tacrolimus doses for atopic eczema are also valid for PN • a 100 g pack of topical tacrolimus delivers the same number of applications as a 100 g pack of TCI The BNF lists tacrolimus doses for one long-term indication (prevention of flares in patients with moderate to severe atopic eczema): apply twice weekly, 0.1% ointment to be applied thinly, with an interval of two to three days between applications. According to this dosing information, the application of tacrolimus is approximately 1/3 less frequent than that assumed for TCS in this model. Therefore, instead of two weeks of use up to 100 g of TCS, PN patients on TCI are assumed to use 100g every six weeks.

BNF = British National Formulary; PN = prurigo nodularis; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids

B.3.5.6.1.2 Rescue medication costs

The cost of the rescue medications was estimated according to the category and frequency medications used by patients in the PRIME2 and PRIME trials.(51, 52) The average acquisition costs of each medication were estimated based on the British National Formulary and are presented in Table 42.(116-120) Treatment duration for each medication was conservatively assumed to be 14 days, except in cases where the drug would be expected to require more than 14 days to take effect or the British National Formulary dose was incompatible with a 14-day course. The average annual cost of rescue medication assumed per patient in the model is £56.12 in BSC arm and £1.52 in the dupilumab plus BSC arm.

Table 42. Average acquisition costs of rescue medication per course (116-119)

	Number of packs / 12-wk cycle	Average acquisition costs / pack, £	Acquisition costs /rescue course, £	BSC patients, %	Dupilumab plus BSC patients, %	*Cost / 12-wk course, £*	
						BSC	***Dupilumab plus BSC***
Dexamethasone	0.50	3.41	1.71	1.9	0.6	0.03	0.01
Prednisolone	1.00	0.85	0.85	0.6	0.6	0.01	0.01
Ciclosporin	14.93	18.37	274.33	2.5	0.0	6.94	0.00
Hydroxychloroquine sulphate	0.23	2.83	0.66	0.6	0.0	0.00	0.00
Methotrexate	0.08	5.39	0.43	0.6	0.0	0.00	0.00

	Number of packs / 12-wk cycle	Average acquisition costs / pack, £	Acquisition costs /rescue course, £	BSC patients, %	Dupilumab plus BSC patients, %	*Cost / 12-wk course, £*	
						BSC	*Dupilumab plus BSC*
Methylprednisolone	0.47	3.88	1.81	1.3	0.0	0.02	0.00
Thalidomide	2.00	298.48	596.96	0.6	0.0	3.78	0.00
Triamcinolone acetonide	0.20	7.45	1.49	0.6	0.0	0.01	0.00
Tramadol	1.87	0.76	1.42	0.0	1.3	0.00	0.02
Tapentadol	2.00	12.46	24.92	0.0	0.6	0.00	0.16
Amitriptyline	1.50	0.7	1.05	0.0	0.6	0.00	0.01
Fexofenadine	0.47	2.01	0.94	0.6	0.0	0.01	0.00
Levocetirizine	0.47	4.37	2.04	0.6	0.0	0.01	0.00
Betamethasone dipropionate 0.1%, cream	1	6.12	6.12	0.0	0.6	0.00	0.04
Fluocinonide 0.05%, cream	1	15.84	15.84	0.6	0.6	0.10	0.10
Calcipotriol 0.005% + betamethasone dipropionate 0.05%, ointment	1	20.50	20.50	1.3	0.0	0.26	0.00
Betamethasone valerate 0.1%, cream	1	5.67	5.67	1	0	0.04	0.00
Clobetasol	1	8.97	8.97	6	0	0.34	0.00
Mometasone	1	8.43	8.43	3	0	0.16	0.00
Tacrolimus	1	62.68	62.68	3	0	1.19	0.00

BSC = best supportive care; wk = week

B.3.5.6.1.3 Background medication costs

Please refer to Appendix K for information on cost of background medications.

B.3.5.6.2 Treatment response state unit costs and resource use

The model considers the disease management costs associated with PN based on treatment response status. Responders are assumed to incur reduced disease management costs.

The inputs for PN (base case) and AD (scenario analysis) define the annual number of each resource used in the BSC and dupilumab arms for responders and non-responders. Unit costs (Table 43) are then applied to this number to estimate the total annual healthcare resource costs (Table 44). The model allows to switch NHS costs between the 2020/21 cost year and the 2019/20 cost year (explored in sensitivity analysis).

Table 43. Health care resource unit costs used in the model

Health care resource	Unit cost, £	Source
GP consultation	39.23	PSSRU, 2021 (GP visit).(115) This is the unit cost of general practitioner visits, including direct care staff costs, with qualification costs, per-patient contact lasting 9.22 minutes.
Dermatology outpatient visit (consultant led)	183.96	The unit cost of a dermatologist visit was estimated to be the weighted average cost for consultant-led dermatology, non-admitted face-to-face follow-up (code WF01A) from the NHS Reference Costs 2020-21(121) (88%) and multi-professional non-admitted face-to-face follow-up attendance cost (12%). Weighting was based on UK market research derived from the previous CEM developed for dupilumab in AD (TA534)(2)
Dermatologist nurse visit	27.50	PSSRU, 2021;(115) assuming 30 minutes of the hourly cost of a nurse of wage band 6
Emergency room visit	332.46	Weighted average unit cost of all A&E attendances where patients received treatment (not all A&E visits receive treatment). Assumes that PN A&E patients all receive treatment. Assumption taken from the Excel model developed previously by Sanofi for atopic dermatitis (TA534)(2) NHS Reference Costs 2020-21(121)
Hospitalisation[a]	2108.95	Value (£1795.29) taken from the model developed previously by Sanofi for AD, (TA534).(2) The value comes from an analysis of the HES database. The cost was inflated using consumer price inflation data from the ONS.[b](90)
Day case	710.57	Average of codes JD07A-JD07K, NHS Reference Costs 2020-21(121)
Full blood count	3.63	National Schedule of NHS Costs 2020-2021; currency = DAPS05(121)
Background medications	221.14	The cost of background medications was estimated by Sanofi (Appendix K). The data were obtained from the previous CEM developed for dupilumab in AD (TA534).(2) Clinical opinion solicited for this appraisal suggested that wash products as well as moisturisers should be considered in the economic modelling. Thus, our estimates about background medication use are conservative. Background medication cost was updated using December 2022 BNF data.(122)
Phototherapy	642.63	National Schedule of NHS Costs 2020-2021, day case, currency = JC47Z (dermatology)(121)
Psychologist	324.94	National Schedule of NHS Costs 2020-2021(121), clinical psychology, consultant-led, non-admitted face-to-face.

AD = atopic dermatitis; CEM = cost-effectiveness model; GP = general practitioner; HES = Hospital Episodes Statistics; NHS = National Health Service; ONS = Office for National Statistics; PSSRU = Personal Social Services Research Unit ; UK = United Kingdom

[a] The cost of hospitalisation was taken from analysis of the HES database in patients with AD, rather than from the NHS Reference Costs. This is firstly because the available HES database values, being in AD, are expected to be more representative of PN, while the data in the NHS Reference Costs are expected to be more generic. Secondly, the choice of HES as the cost data source for hospitalisation was also influenced by expert opinion. Both clinical and health economics experts, interviewed as part of the development process of the present model, indicated that the hospitalisation cost from HES appears too expensive. Yet, the HES cost is considerably lower than the cost in the NHS Reference Costs. Therefore, by using the HES cost, the model is using the lower of the two available hospitalisation costs.

[b] This is a conservative approach. The unit cost from NHS Reference Costs 2020-21 for non-elective dermatology inpatient visits, the average cost of hospitalisation (non-elective dermatology inpatients) is ca. £3,000.

Table 44. Health care resource cost applied in the model

Indication	Response status	Annual resource cost, £	Source
PN (base case)	Responder	1,358.75	Calculated by multiplying the frequency of use of each healthcare resource for responders and non-responders (Table 35) by
	Non-responders	2,952.36	

Indication	Response status	Annual resource cost, £	Source
			the unit price of each resource (Table 43)
AD (scenario analysis)	Responder	1,788.80	Calculated by multiplying the frequency of use of each healthcare resource for responders and non-responders (Table 36) by the unit price of each resource (Table 43)
	Non-responders	3,422.60	

AD = atopic dermatitis; PN = Prurigo Nodularis

B.3.5.6.3 Adverse reaction unit costs and resource use

The AEs considered in the model are based on those reported in the dupilumab clinical trials. Data are trial specific and the incidence of these events for the PRIME2 and PRIME trials is shown in Table 45. AE costs were incurred at every model cycle. Patients who received only one therapy (e.g., BSC only) were assigned the AE cost of that therapy (e.g., BSC only). Patients who received two therapies (e.g., dupilumab and BSC) only incurred one AE cost. They were assigned the more expensive of the two AE costs, if applicable. As patients received both treatments, this is reflective of the clinical trial.

The costs for AEs applied to the dupilumab and BSC arms of the model were calculated as weighted averages based on the inputs presented in Table 45. The obtained values were further linearly extrapolated to one year to yield AE costs for dupilumab (£34.24) and for BSC (£2.44) (Table 45).

Table 45. AE inputs used in the model

	Proportion experiencing AEs over 24 weeks' clinical trial			Unit cost (£)	
	Dupilumab plus BSC, %	**BSC, %**	**Source**	**Unit cost (£)**	**Assumption (Source)**
Allergic conjunctivitis	4.04	1.11	PRIME2 and PRIME clinical trials(54)	39	GP visit(115)
Injection site reaction	6.06	0		184	Consultant visit(121)
Skin infection	1.01	0		39	GP visit(115)
Oral herpes	2.02	0		39	GP visit(115)
Infectious conjunctivitis	3.03	1.11		94	GP visit + consultant visit(115, 121)
All AEs	**Dupilumab plus BSC, £**	**BSC, £**			
Cost per year	36.46	3.22			

AE = adverse event; BSC = best supportive care; GP = general practitioner

B.3.5.6.4 Indirect costs

Indirect costs were not included in the base-case analysis because a healthcare payer's perspective was used. The model allows users to include indirect costs (out-of-pocket costs

and/or productivity costs) based on response status when the analysis is conducted from a societal perspective. These are discussed below.

B.3.5.6.4.1 Productivity costs

The effect of including indirect costs on the ICER is presented in scenario analysis. In order to do this, productivity loss inputs (Table 46) are applied to the employment parameters tabulated below (Table 47) to estimate the indirect costs. Due to the lack of published data regarding productivity loss in patients with PN, the model used estimates from the dupilumab AD model which is the best available evidence and results in productivity loss costs of £930 PPPY for responders and £4,267 PPPY for non-responders (Table 48).(2)

Table 46. Productivity loss inputs

Productivity loss	Responder	Non-responder	Source
Absenteeism (days per month)	0.98	4.48	Estimated days missed and expenses for mild (responders) and severe (non-responders) AD from the AWARE study.(2) Presenteeism was not collected in the study. Thus, these inputs are set to zero.

AD = atopic dermatitis

Table 47. Employment parameters

Employment parameters	Input	Source
Value of productivity loss per hour	£16.52	Weighted average of full- and part-time employment wages per hour using data from the Office for National Statistics (2021, 2022c).
Percentage employed	78.5%	Percentage of employed participants in the AWARE study.(2) Similar to the percentages in SOLO1+2 (72.4%), CHRONOS (76.6%) and CAFÉ (76.6%).(2)
Working hours per day	6.13	Weighted average of full- and part-time employment hours per workday using data from the UK ONS(123)

ONS = Office for National Statistics; UK = United Kingdom

Table 48. Productivity costs used in the model

Patients with PN	PPPY, £
Treatment responders	930
Treatment non-responders	4,267

PN = prurigo nodularis; PPPY = per patient per year

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A summary of the inputs and variables used in the cost-effectiveness analysis of the base case is in Table 49.

Table 49. Summary of the base-case variables applied in the economic model

Variable	Value	Measurement of uncertainty (distribution)	Reference/corresponding section in this report
Model characteristics			
Perspective	Healthcare payer (NHS and personal social services (PSS)	N/A	NICE reference case(124)
Patient population	Full licence patient population	N/A	N/A
Time horizon	Lifetime (50 years)	N/A	Assumption
Discount rate: costs and outcomes	3.5%	N/A	NICE manual(89)
Patient characteristics			
Mean age, years	49.5	SE = 0.91 (lognormal)	PRIME2 and PRIME pooled data (Table 9)(53)
Males, %	34.7	n/N = 108/311 (beta)	
Body weight, kg	73.9	SD = 17.9 (lognormal)	
Baseline EQ-5D-5L utility estimated based on algorithm by Hernández Alava (2020)	[redacted]	SE = 0.01 (beta)	
Age-specific mortality rate	UK national life tables rates by age and sex	N/A	ONS(95)
Response rates			
Decision tree			
Response criteria	WI-NRS improvement (reduction) ≥4 from baseline and IGA-PN-S score from baseline (≥ 1)	N/A	Assumption
Percentage of dupilumab plus BSC responders at Week 24	[redacted]	n/N = 90/153 (beta)	PRIME2 and PRIME pooled data(53); response criteria: WI-NRS improvement ≥4 and IGA-PN-S reduction ≥1 (Section B.3.3.2.1)
Percentage of BSC responders at Week 24	[redacted]	n/N = 30/158 (beta)	
Discontinuation rate			
Markov model			
Dupilumab annual other-cause discontinuation	[redacted]	Beta	PRIME2 and PRIME pooled data(53)
BSC discontinuation rate	[redacted]	Beta	PRIME2 and PRIME pooled data(53)
Utility (EQ-5D-5L)			
Utility value set	Estimated based on a mixed-model regression	Cholesky and uncertainty in the patient baseline characteristics	Section B.3.4.2.1
Decision tree			
Utility weight during Weeks 0-12 for all patients	[redacted]	Cholesky decomposition	Baseline utility of all patients based on algorithm by Hernández Alava(91)
Utility weight during Weeks 12-24 for all dupilumab plus BSC patients	[redacted]	Cholesky decomposition	Week 12 utility of all dupilumab plus BSC patients generated by a regression model (Section B.3.4.2.1)

Variable	Value	Measurement of uncertainty (distribution)	Reference/corresponding section in this report
Utility weight during Weeks 12-24 for all BSC patients	[redacted]	Cholesky decomposition	Week 12 utility of all BSC patients generated by a regression model (Section B.3.4.2.1)
Markov model			
Utility weights for dupilumab plus BSC patients in the 'Response' treatment state	[redacted]	Cholesky decomposition	Week 24 utility of dupilumab responders generated by a regression model (Section B.3.4.2.1)
Utility weights for dupilumab plus BSC patients in the 'No Response' treatment state	[redacted]	Cholesky decomposition	Week 24 utility of dupilumab non-responders generated by a regression model (Section B.3.4.2.1)
Utility weights for BSC patients in the 'Response' treatment state	[redacted]	Cholesky decomposition	Week 24 utility of BSC responders generated by a regression model (Section B.3.4.2.1)
Utility weights for BSC patients in the 'No Response' treatment state	[redacted]	Cholesky decomposition	Week 24 utility of all BSC Non-Responders generated by a regression model (Section B.3.4.2.1)
Utility waning: dupilumab plus BSC patients	Enabled, Year 2: 91.4% Year 3: 97.2% Year 4: 90.9% Year 5+: 90.9%	N/A	AD OLE study(55, 78) (see Appendix T for summary of study)
Utility waning: BSC patients	Enabled, Year 2: 75.0% Year 3: 50.0% Year 4: 25.0% Year 5+: 0.0%	N/A	Estimates provided by NICE for AD(2)
Costs			
Dupilumab drug-acquisition costs, £			
Patient access scheme cost of two 300 mg pre-filled syringes	[redacted]	Not varied in sensitivity analysis	Reference table in submission
Dupilumab 300 mg in Year 1	[redacted]	Not varied in sensitivity analysis	Reference table in submission
Dupilumab 300 mg in Year 2+	[redacted]	Not varied in sensitivity analysis	Reference table in submission
Dupilumab dosing regimen	Q2W	N/A	PRIME2 and PRIME trial protocols(53)
BSC drug-acquisition costs, £			
Average acquisition costs of a 100 g pack of TCS	34.95	Fixed	See Table 39
Average acquisition costs of a 100 g pack of TCI	62.68	Fixed	See Table 39
TCS and TCI treatment frequencies	TCS: 100g Q2W	Fixed	See Table 41

Variable	Value	Measurement of uncertainty (distribution)	Reference/corresponding section in this report
	TCI: 100g every six weeks		
Dupilumab drug administration costs, £			
Unit cost per subcutaneous administration/training	55	Fixed	PSSRU, 2021;(115) assumed dupilumab to be self-administered following an hour of instruction from a nurse
Disease management cost, £			
Average annual disease management cost for patients in the 'Response' treatment state, £	1,358.75	Gamma	Section B.3.5.6.2
Average annual disease management cost for patients in the 'No Response' treatment state, £	2,952.36	Gamma	Section B.3.5.6.2

AD = atopic dermatitis; BSC = best supportive care; CEM = cost-effectiveness model; DLQI = Dermatology Life Quality Index; EQ-5D-5L = EuroQol five -dimensions five-levels; IGA-PN-S = Investigator's Global Assessment for Prurigo Nodularis –Stage; N/A = not applicable; NICE = National Institute for Health and Care Excellence; NHS = National Health Service; NRS = numeric rating scale; OLE = open-label extension; ONS = Office for National Statistics; PSS = personal social services; PSSRU = Personal Social Services Research Unit; Q2W = every two weeks; SE = standard error; TCS = topical corticosteroids; TCI = topical calcineurin inhibitors; UK = United Kingdom; WI-NRS = The Worst-Itch Numeric Rating Scale

B.3.6.2 Assumptions

Assumptions made in the model base case are summarised in Table 50.

Table 50. Summary of assumptions and corresponding rationale

Description of assumption used in the base case	Justification
A 12-week cycle length is assumed in the Markov model	A half-cycle correction using the life method is applied in the Markov model to account for the fact that events and transitions can occur at any point during the cycle, not necessarily at the start or end of each cycle.
All-cause treatment discontinuation is used as a proxy for loss of response. Trial-observed discontinuation rates are used as transition probabilities from 'response' to 'non-response'	Endorsed by clinicians in global advisory board in April 2022.(63)
Long-term response rates are assumed to be similar between AD and PN	Long-term response data are not available for PN. Based on clinician input, response to BSC observed in the PRIME2 and PRIME trials is unlikely to be maintained after trial end. However, dupilumab response while still on treatment, would be maintained post trial and based on the OLE study data for AD (Appendix T) (55, 78) and clinical experience, there is no reason to believe that the HRQoL of patients who continue to respond to dupilumab would decrease over time.(73) The OLE for AD is the most robust data available for treatment with dupilumab in a similar disease area and was confirmed as the preferred data for response waning with dupilumab in the global advisory board conducted in April 2022.(63)

Description of assumption used in the base case	Justification
Absenteeism is assumed to be similar to AD	Because PN is also a rare disease, the extent of absenteeism is assumed to be similar between AD and PN which are analogous diseases.
No AE disutilities in model	To avoid double counting and given the frequency of EQ-5D assessment, disutility because of AEs is assumed to be accounted for within patient-level EQ-5D responses collected during the PRIME2 and PRIME trials
Patients do not have an increased risk of mortality due to PN	There is little evidence to suggest PN has a significant impact on mortality.(125)
Doses prescribed for TCS and TCIs assumed to be similar between their licensed indications listed in the BNF and PN	Because PN is also a rare disease, the estimates for per-patient use of TCS and TCIs are based on the BNF's prescribing recommendations to clinicians (due to the absence of precise relevant data from clinical trials)
Cost of TCS and TCIs assumed to be the average of the cost of the individual corticosteroid creams and ointments available in the BNF	

AD = atopic dermatitis; AE = adverse event; BNF = British National Formulary; BSC = best supportive care; EQ-5D-5L = EuroQol five -dimensions; HRQoL = health-related quality of life; OLE = open-label extension; PN = prurigo nodularis; TCI = topical calcineurin inhibitors; TCS = topical corticosteroids

B.3.7 Base-case results

The expected positioning of dupilumab in UK clinical practice is for the treatment of adults with moderate-to-severe PN who are candidates for systemic therapy.(51, 52) In line with this full licence positioning, we present results for the full analysis sets for the pooled PRIME2 and PRIME populations below. The base-case results are calculated based on the key parameters listed in Table 49 above. Base case results are presented in Table 51. Disaggregated results are presented in Appendix J.

At patient access scheme price, BSC and dupilumab accumulated costs of [redacted] and [redacted], and total quality-adjusted life-years (QALYs) of [redacted] and [redacted], respectively. The ICER was within the range considered cost-effective at £26,776 per QALY, as it falls below the conventional NICE willingness-to-pay threshold of £30,000 per QALY.

These results demonstrate that dupilumab is an appropriate use of NHS resources. Particularly notable is the scale of QALY gain given this is a therapy that does not impact life expectancy. As such, this gain represents a substantial and long-term improvement in patient HRQoL, both reflective of the benefit of dupilumab in improving symptoms of itch and the poor starting health state for patients with moderate-to-severe PN.

Table 51. Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Probabilistic (base case)							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,886
Deterministic							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,879

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years

B.3.8 Exploring uncertainty

B.3.8.1 Probabilistic sensitivity analysis

The parameters and their distributions used in the probabilistic sensitivity analysis are specified in Table 49 above. The probabilistic results are presented Table 51, Figure 18 and Figure 19. Results show that at a willingness-to-pay (WTP) of £30,000, the probability of being cost-effective is [redacted]; at £20,000 it is [redacted].

Figure 18. Cost effectiveness acceptability curve (10,000 iterations)

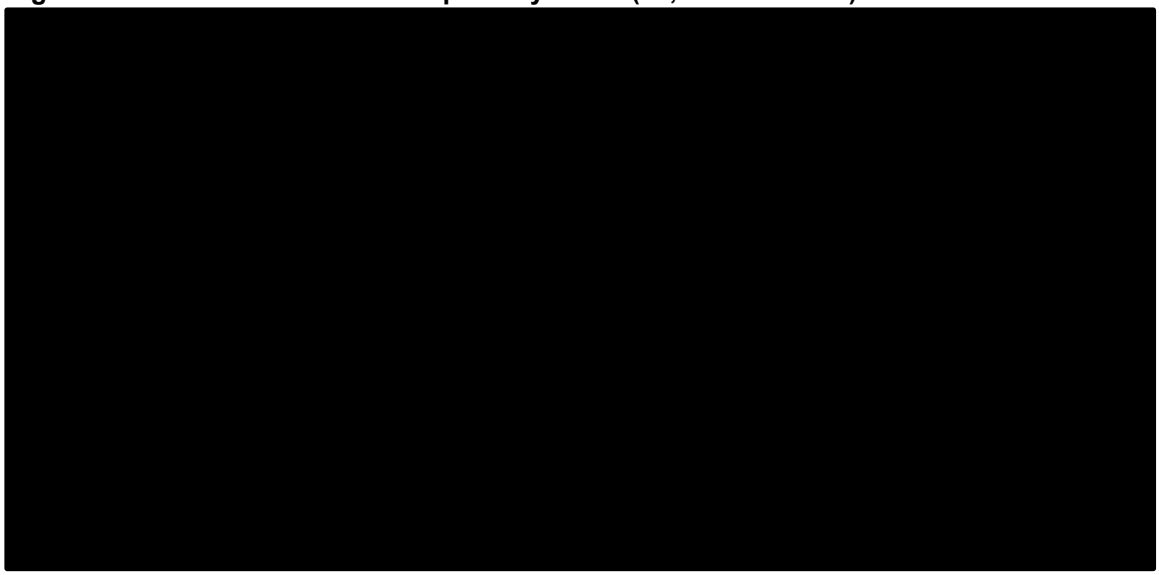


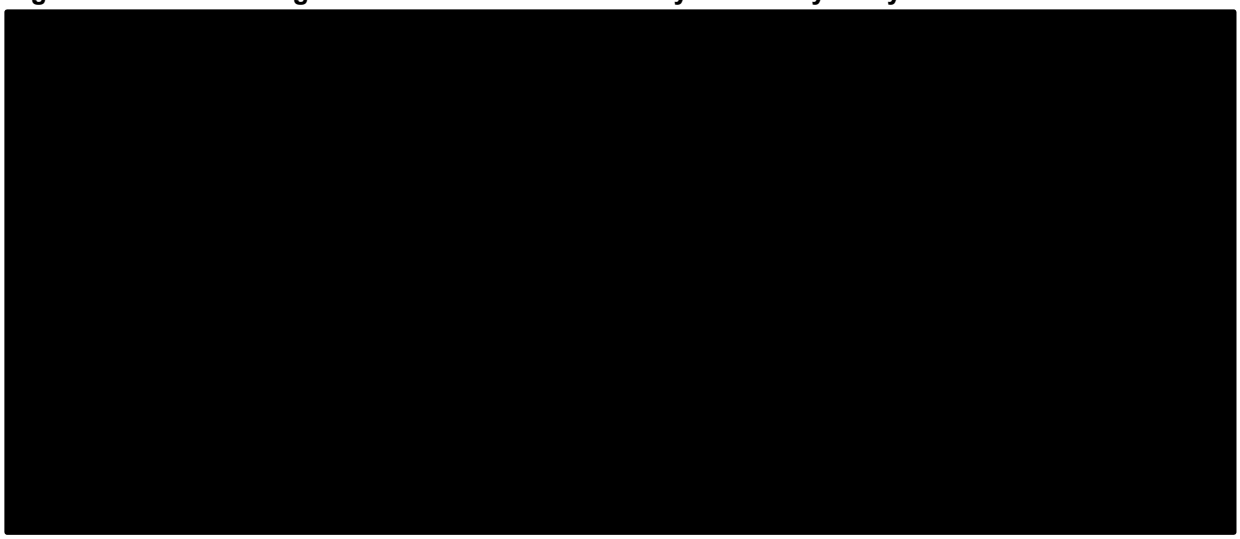
Figure 19. Scatter plot for incremental cost effectiveness results (10,000 iterations)

CE = cost-effectiveness; QALYs = quality-adjusted life years

B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were undertaken to explore the impact of changing assumptions concerning key model parameter values on the base case ICERs. In the DSA, inputs were varied by their 95% CIs to represent upper and lower bounds where these data were available. Where 95% CIs were not available, a variation of ± 10% of the mean was assumed. The ten most influential variables in the DSA for the analysis of dupilumab plus BSC (patient access scheme price) versus BSC are presented as tornado plot in Figure 20. These results indicate that the three most influential parameters on the ICER results at a £30,000 threshold were baseline utility, change in utility, and response waning. Overall, results were robust to parameter uncertainty, demonstrating the stability of the model.

Figure 20. Tornado diagram for deterministic one-way sensitivity analysis



HRU = healthcare resource use; PN = prurigo nodularis

B.3.8.3 Scenario analysis

A number of scenario analyses were explored in which model assumptions or parameters were altered. The rationale and results of the scenario analyses carried out are presented in Table 52. Overall, results were robust to alternative assumptions and parameters, demonstrating the stability of the model.

Table 52. Scenario analyses

Scenario	Rationale	Incremental costs	Incremental QALYs	ICER
Response criteria: WI-NRS improvement ≥4	Testing sensitivity to alternative response criteria	[redacted]	[redacted]	28,210
No response waning applied	Testing sensitivity to inclusion of response waning	[redacted]	[redacted]	26,851
Response waning AD Dermatologist survey + SEE	Testing sensitivity to values of response waning	[redacted]	[redacted]	28,082
Response waning AD Dermatologist survey + NICE estimates	Testing sensitivity to values of response waning	[redacted]	[redacted]	28,262
Response waning AD OLE study + SEE	Testing sensitivity to values of response waning	[redacted]	[redacted]	26,544
Inclusion of societal perspective	Testing sensitivity to inclusion of productivity loss	[redacted]	[redacted]	12,158
HCRU – AD micro-costing	Testing sensitivity to alternative cost values	[redacted]	[redacted]	26,661
HCRU – PN micro costing based on 2019/2020 cost data	Testing sensitivity to alternative cost values	[redacted]	[redacted]	27,652
HCRU-TA814	Testing sensitivity to alternative cost values	[redacted]	[redacted]	27,389
HCRU-TA534	Testing sensitivity to alternative cost values	[redacted]	[redacted]	23,255
Utility algorithm: Van Hout	Testing sensitivity to alternative utility values	[redacted]	[redacted]	24,148
AD discontinuation rate	Testing sensitivity to discontinuation assumptions	[redacted]	[redacted]	26,218

AD = atopic dermatitis; HCRU = healthcare resource use; 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 numeric rating scale

B.3.8.4 Subgroup analysis

No economic subgroup analyses were conducted as part of this submission.

B.3.8.5 Summary of Scenario and Sensitivity Analysis

Results of the sensitivity analysis demonstrate that the base case cost-effectiveness results exhibit little variation when the combined distributional uncertainty across model parameters is taken into account. The DSA results aligned closely with the probabilistic base case results showing that dupilumab plus BSC is cost-effective versus BSC alone and indicating it to be a cost-effective use of resources in the NHS. Limited variation was observed in the majority of changes to the modelling approach that were explored in the scenario analyses: across all scenarios conducted, dupilumab was associated with ICERs of less than £30,000 per QALY gained. Taken together, these results demonstrate the robustness of the model to uncertainty.

B.3.9 Benefits not captured in the QALY calculation

Dupilumab offers significant benefits to patients and society that are not captured in the QALY. Social functioning is not included in the descriptive system in EQ-5D but is an important aspect of disease burden. Importantly, it may have significant impact on productivity, which is captured in the model as indirect costs. For example, it is likely that dupilumab which significantly reduces pruritus and sleep loss, will enable patients to return to work or take fewer days off with associated productivity gains (the average number of days of work lost per month for severe AD [non-responders] from the AWARE study was 4.48 compared to 0.98 days per month for mild AD [responders]).(2)

A patient testimony from an interview with a PN patient conducted by Sanofi in October 2022 highlights the impact of PN on patients' relationship, social and working life.(14) In particular, the patient made the following comments on sleep, mood, time for self-care and impact on daily schedule when working:

- 'Having nodular prurigo **affects my life**, it's always in the front of my mind so if I'm having visitors over and I'm having a flare then I would cancel it.'
- '[PN] impact my ability to **sleep** if you have a particularly painful nodule. I would suggest it impacts on my sleep half of the week. If I'm having a flare-up then that will impact greatly.'
- '[PN] impacts on your **mood** because you're tired.'

- ‘I have **depression** and **anxiety**: the nodular prurigo doesn’t help with that because I’m anxious about people thinking about what I look like. 50 percent of my depression and anxiety is linked to nodular prurigo.’
- ‘On average it’s two hours a day, so 14 hours a week doing **self-care** of my nodular prurigo. If I have a big flare, I may have to spend extra time applying lotions, taking antibiotics or extra painkillers and shaving my hair: this add another hour a day, so 21 hours a week.’
- ‘Living with nodular prurigo affects my daily schedule all the time. I have to **get up earlier to get ready for work** – shower, moisturise, shave my head if needed and put my “work face” on.’

Furthermore, PN impacts the HRQoL of people who care for patients with PN. Sanofi interviewed the carer (partner) of the above patient with PN who described the experience of being physically unable to do anything to stop the patient’s pain as ‘upsetting’.(44) PN was also noted to have a ‘major impact’ on social activities together and the carer described PN as ‘frustrating’ and ‘challenging’ from a mental health perspective.(44)

Cost-effectiveness results from the PN model which include indirect costs are presented in Table 53.

Table 53. Probabilistic results with the inclusion of indirect costs (10,000 iterations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,158

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years

B.3.10 Validation

B.3.10.1 Clinical validation

Expert clinical input was sought during the development of the cost-effectiveness model to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice and to validate the clinical plausibility of the outcomes predicted by the model. Feedback was obtained in two advisory boards and in total, input was gathered from three UK clinical experts. As detailed throughout the submission, the clinical experts agreed with the approaches and assumptions taken in the development of the cost-effectiveness model. Expert clinical opinion was sought to validate the following model inputs:(1, 63)

- Model structure

- Response criteria
- All-cause discontinuation used as proxy for loss of response
- Long-term effect and response waning
- Utilities calculation based on linear regression equations
- Treatment cost categories and HCRU for patients with PN.

B.3.10.2 Technical validation

The model was subjected to a thorough validation process in accordance with guidelines for validation put forth by the International Society for Pharmacoeconomics and Outcomes Research Society and the Society for Medical Decision-Making Joint Task Force for Modelling Good Research Practices.(126) These guidelines stress the importance of face validity (confirming the model approach, data sources and assumptions with experts), internal validity (quality-checking of parameter values and calculations) and external validity (comparing model results with other published studies).

Face validity was tested throughout model development with external health economic and clinical experts during two advisory boards conducted by Sanofi.(1, 63) Internal validity was tested by researchers not involved in model development checking the accuracy of all data extracted from the literature, the logical structure of the model and the accuracy of all calculations and programming (for the detailed report see Appendix R). Additionally, the researchers conducting the quality control review, in collaboration with the model developers, subjected the model to a series of diagnostic tests to ensure that the model reacted as expected. External validation was not possible as this is the first cost-effectiveness model for long-term treatment with a biologic in PN. All other cost-effectiveness models identified were for short-term treatment of PN and were not relevant comparisons to this model.

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 Conclusions from the cost-effectiveness analysis

Patients with PN have a substantial clinical, humanistic and economic burden. There is a high unmet need for a targeted, efficacious, and safe treatment for these patients. Currently no approved targeted systemic therapies are available for PN aside from dupilumab. All prescribed off-label and non-targeted systemic therapies for PN lack supportive randomised

controlled evidence and are associated with safety and tolerability concerns (see Section B.1.3.2). Dupilumab will be the first licenced systemic medicine with a robust evidence base targeted against the disease. The PRIME2 and PRIME trials are the largest PN clinical trials conducted to date and demonstrate the efficacy and tolerability of dupilumab versus BSC in improving symptoms of PN. Pooled safety data from the trials were consistent with the established safety profile of dupilumab in other indications; over 500,000 patients have been treated with dupilumab in total, with an estimated cumulative patient exposure of all dupilumab treated patients in clinical practice of 706,212 patient years.(76, 77)

The economic analysis described in this section presents a robust case for the value of dupilumab as a treatment for PN. Dupilumab was cost-effective when compared to BSC for the treatment of adult patients with moderate-to-severe PN who are candidates for systemic therapy, with an incremental QALY gain of [redacted] and an ICER of £26,886 per QALY (patient access scheme price).

The model structure and inputs are robust, as validated by UK clinicians. Assumptions included in the model were tested with extensive scenario and sensitivity analyses which demonstrated that the base-case ICER is stable to variation in inputs and structural assumptions. Based on the probabilistic sensitivity analysis, there is a high likelihood ([redacted]) that dupilumab is cost-effective versus BSC with a WTP threshold of £30,000.

There are uncertainties around the benefit of dupilumab due to the low prevalence of PN (3.27 per 10,000 in England), which is considered a rare disease in the UK.(10, 11) Systematic literature searches highlight the limited evidence on treatment efficacy in PN, HRQoL and utilities in patients with PN, and the costs and HRCU associated with PN. To date, no economic evaluations of treatments for PN have been published. Moreover, indirect costs were not included in the base-case analysis as it was conducted from a healthcare payer perspective. Nevertheless, dupilumab offers significant benefits to patients and society that are not captured in the QALY, including work productivity and social functioning. It is likely that the significant reduction in pruritis and sleep loss afforded by dupilumab will enable patients to return to work faster and take fewer days off. Improvements in HRQoL increased over time in the OLE study of dupilumab in the analogous disease area of AD (Appendix T); similar improvement in HRQoL is expected for patients with PN.

Dupilumab represents a cost-effective use of NHS resource for patients with PN compared with current therapy and would address a considerable unmet need for a targeted, systemic therapy for this highly burdened population.

B.3.11.2 Generalisability to clinical practice

The base-case population reflects the anticipated UK population and is derived directly from randomised controlled evidence for dupilumab in PN (Section B.1 and Section B.2).

The patient populations included in the PRIME2 and PRIME trials, and in the economic analysis, reflect the PN patient population expected in clinical practice. The dupilumab studies included adults with moderate-to-severe PN affecting a large portion of their BSA. They experienced high levels of PN symptoms, including pruritus. Their disease could not be adequately controlled with topical prescription medications, or otherwise topical mediations were not advised due to important side effects or safety risks. This population included patients who had been, or would typically be, candidates for systemic PN therapies. In the real word, previous treatment history (encompassing inadequately effective, not tolerated or contraindicated therapies; i.e., medically inadvisable) coupled with clinician opinion, serves as a holistic assessment for eligibility for treatment with dupilumab.

B.3.11.2.1 Holistic assessment of efficacy response in the model

We have implemented the outcomes measured in the study programme in the economic model while capturing improvements in the key disease characteristics important to patients and clinicians to support clinical decision making. According to UK clinicians, a measure of response which captures clinical signs alongside HRQoL improvement is required; improvement in clinical signs (such as skin clearance) alone is not comprehensive enough. Improvement in WI-NRS and IGA-PN-S scores are generally regarded as distinct clinical benefits, particularly in patients with moderate-to-severe PN for whom topical therapy has failed and for whom systemic immunosuppressants are contraindicated, intolerable, provide inadequate response or are otherwise medically inadvisable. Hence, WI-NRS improvement ≥4 from baseline and IGA-PN-S score ≥ 1 from baseline are used as proxies for holistic assessment of efficacy response in the modelling, as endorsed by UK clinical experts in advisory boards conducted by Sanofi in 2022 (Section B.3.5.3 Advisory board to evaluate UK clinicians' perceptions of healthcare resource use).(1, 63) As with the previously accepted efficacy response criterion for the AD assessments carried out by NICE, this is a post-hoc endpoint developed to reflect UK practice and which demonstrated statistically significant results in the full licence population versus BSC, justifying its use in the economic case.

B.3.11.2.2 Strength – use of RCT evidence to reflect clinical practice

The PRIME2 and PRIME trials are robust studies in a rare disease area where there has been a paucity of evidence to date. A key feature of the trials was that the study designs

closely reflect clinical practice and allowed trial participants to receive rescue therapy in response to an exacerbation. We have used the 'all observed' data from the trial in the economic analysis (including patients requiring rescue treatment and using TCS) as this retains as much of the trial data as possible and most closely reflects expected real world clinical practice.

B.3.11.2.3 Limitation – long-term follow-up

The key efficacy outcomes in the PRIME2 and PRIME trials were measured up to 24 weeks, as per regulatory requirements. However, many patients including those with the greatest potential to benefit, may require longer to reach a specified response threshold, especially as it can be expected that PN nodules take longer to resolve, compared with disease resolution in AD. This continuous effect of dupilumab in PN is consistent with results from the dupilumab OLE study in AD (Appendix T), which included 1,419 patients with moderate-to-severe AD treated with dupilumab (55, 72). The efficacy of dupilumab in patients with moderate-to-severe AD improved continuously from Week 2 to Week 52 and improvements (including in HRQoL) were observed up to Week 204 in the OLE study. These results suggest that long-term efficacy benefits of dupilumab in PN may continue beyond Week 24, as supported by clinician input (Section B.3.3.2.2.3 and Section B.3.5.3 Advisory board to evaluate UK clinicians' perceptions of healthcare resource use).(55, 72) Because of the paucity of evidence on PN and the rarity of PN, many assumptions in the model were taken from analogous diseases (primarily AD). This was supported by extensive clinician input (55, 72) and was tested in scenario analysis.

B.3.11.2 Summary

Dupilumab addresses the high unmet need for a targeted, systemic treatment for patients with PN who incur substantial clinical, humanistic and economic burden. Dupilumab demonstrated clinically and statistically significant improvements in the signs and symptoms of PN, as well as HRQoL, in the PRIME2 and PRIME trials, with an acceptable benefit-risk profile.

The value of dupilumab was established in a robust economic analysis where dupilumab was shown to be a cost-effective treatment for PN at a WTP threshold of £30,000 for the expected population. The ICER results were consistent when tested against a range of key model inputs and assumptions. Incremental QALY gains were generally in the range of [redacted] to [redacted], with incremental ICERs clustered below the £20,000 to £30,000 WTP threshold at the patient access scheme price. Because of the rarity of PN in the population, the budget impact is projected to be low ([redacted] in 2024; Document C).

The QALY gains represent a substantial and long-term improvement in patient HRQoL, both reflective of the benefit of dupilumab in improving symptoms of itch and the poor starting health state for patients with moderate-to-severe PN. It should be emphasised that a QALY gain near 1.0 in a treatment that is not life extending is a remarkable result. Furthermore, additional benefit not captured in the QALY gains is expected with dupilumab.

UK dermatologists who participated in advisory boards conducted by Sanofi in 2022 were *'impressed'* with the benefits of dupilumab in PN and expressed their interest in using dupilumab for their patients.(63)

B.4 References

1. Sanofi. Data on file. Advisory Board Notes (12 December 2022). 2022.
2. National Institute for Health and Care Excellence. Dupilumab for treating moderate to severe atopic dermatitis (TA534). 2018.
3. Sanofi. Summary of Product Characteristics (Dupixent). https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf. 2023.
4. Zeidler C, Tsianakas A, Pereira M, Stander H, Yosipovitch G, Stander S. Chronic Prurigo of Nodular Type: A Review. Acta Derm Venereol. 2018;98(2):173-9.
5. Zeidler C, Yosipovitch G, Stander S. Prurigo Nodularis and Its Management. Dermatol Clin. 2018;36(3):189-97.
6. Mack MR, Kim BS. The Itch-Scratch Cycle: A Neuroimmune Perspective. Trends Immunol. 2018;39(12):980-91.
7. Pereira MP, Steinke S, Zeidler C, Forner C, Riepe C, Augustin M, et al. European academy of dermatology and venereology European prurigo project: expert consensus on the definition, classification and terminology of chronic prurigo. J Eur Acad Dermatol Venereol. 2018;32(7):1059-65.
8. Pereira MP, Hoffmann V, Weisshaar E, Wallengren J, Halvorsen JA, Garcovich S, et al. Chronic nodular prurigo: clinical profile and burden. A European cross-sectional study. Journal of the European Academy of Dermatology and Venereology. 2020.
9. Leis M, Fleming P, Lynde CW. Prurigo Nodularis: Review and Emerging Treatments. Skin Therapy Lett. 2021;26(3):5-8.
10. Department of Health & Social Care. Policy paper. The UK Rare Diseases Framework. https://www.gov.uk/government/publications/uk-rare-diseases-framework/the-uk-rare-diseases-framework. 2021.
11. Morgan CL, Thomas M, Ständer S, Jabbar-Lopez ZK, Piketty C, Gabriel S, et al. Epidemiology of prurigo nodularis in England: a retrospective database analysis. Br J Dermatol. 2022.
12. Sanofi. Dupixent (dupilumab). Patient Funnels.; 2021.
13. Sanofi. Dupixent (dupilumab). Patient Funnels. 2022.
14. Sanofi. Data on file. Prurigo nodularis case study. 2022.
15. Pereira MP, Basta S, Moore J, Stander S. Prurigo nodularis: a physician survey to evaluate current perceptions of its classification, clinical experience and unmet need. Journal of the European Academy of Dermatology and Venereology. 2018;32(12):2224-9.
16. Todberg T, Zachariae C, Skov L. Treatment and burden of disease in a cohort of patients with prurigo nodularis: A survey-based study. Acta Dermato-Venereologica. 2020;100(8):1-5.
17. Sanofi. Nodular Prurigo Patient Journey Research (Phases 2 & 3) (data on file). 2020.
18. Grundel S, Pereira MP, Storck M, Osada N, Schneider G, Stander S, et al. Analysis of 325 Patients with Chronic Nodular Prurigo: Clinics, Burden of Disease and Course of Treatment. Acta dermato venereologica. 2020;17.
19. Kowalski EH, Kneiber D, Valdebran M, Patel U, Amber KT. Treatment-resistant prurigo nodularis: challenges and solutions. Clin Cosmet Investig Dermatol. 2019;12:163-72.

20. Stander HF, Elmariah S, Zeidler C, Spellman M, Stander S. Diagnostic and treatment algorithm for chronic nodular prurigo. J Am Acad Dermatol. 2020;82(2):460-8.
21. Ständer S, Pereira MP, Berger T, Zeidler C, Augustin M, Bobko S, et al. IFSI-guideline on chronic prurigo including prurigo nodularis. Itch. 2020;5(4):e42.
22. Huang AH, Canner JK, Kang S, Kwatra SG. Analysis of real-world treatment patterns in patients with prurigo nodularis. Journal of the American Academy of Dermatology. 2020;82(1):34-6.
23. Pereira MP, Zeidler C, Wallengren J, Halvorsen JA, Weisshaar E, Garcovich S, et al. Chronic Nodular Prurigo: A European Cross-sectional Study of Patient Perspectives on Therapeutic Goals and Satisfaction. Acta Derm Venereol. 2021;101(2):adv00403.
24. Labib A, Ju T, Vander Does A, Yosipovitch G. Immunotargets and Therapy for Prurigo Nodularis. Immunotargets Ther. 2022;11:11-21.
25. Bedoui Y, Guillot X, Sélambarom J, Guiraud P, Giry C, Jaffar-Bandjee MC, et al. Methotrexate an Old Drug with New Tricks. Int J Mol Sci. 2019;20(20).
26. Kelly P, Kahan BD. Review: metabolism of immunosuppressant drugs. Curr Drug Metab. 2002;3(3):275-87.
27. Garcovich S, Maurelli M, Gisondi P, Peris K, Yosipovitch G, Girolomoni G. Pruritus as a Distinctive Feature of Type 2 Inflammation. Vaccines (Basel). 2021;9(3).
28. Furue M, Furue M. Interleukin-31 and Pruritic Skin. J Clin Med. 2021;10(9).
29. Sanofi. Data on file. NHS England Commercial Surgery Dupixent. 2022.
30. Iking A, Grundmann S, Chatzigeorgakidis E, Phan NQ, Klein D, Stander S. Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. J Eur Acad Dermatol Venereol. 2013;27(5):550-7.
31. Tan WS, Tey HL. Extensive prurigo nodularis: Characterization and etiology. Dermatology. 2014;228(3):276-80.
32. Kwon CD, Khanna R, Williams KA, Kwatra MM, Kwatra SG. Diagnostic Workup and Evaluation of Patients with Prurigo Nodularis. Medicines. 2019;6(4):26.
33. British Association of Dermatologists (BAD). Nodular Prurigo (patient information leaflet). 2020.
34. Sanofi. Nodular Prurigo Patient Journeys (data on file). 2020.
35. Sanofi. Healthcare database study to estimate prevalence and healthcare burden of prurigo nodularis (data on file). 2022.
36. Bahloul D, Conlon S, Thomas RB, Diribe O, McDonald R, Mathias E, et al., editors. A retrospective database study to describe the prevalence, patient characteristics and healthcare burden of prurigo nodularis (PN) in England (poster). International Society for Pharmacoeconomics and Outcomes Research (ISPOR) - EU 2022 (November 6–9, 2022); 2022; Vienna, Austria.
37. ONS. Principal projection - England summary. 2020-based interim national population projections. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/datasets/tablea14principalprojectionenglandsummary. 2022.
38. ONS. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2020. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/pop

ulationestimates/bulletins/annualmidyearpopulationestimates/mid2020#age-structure-of-the-uk-population. 2021.
39. Jorgensen KM, Egeberg A, Gislason GH, Skov L, Thyssen JP. Anxiety, depression and suicide in patients with prurigo nodularis. J Eur Acad Dermatol Venereol. 2017;31(2):e106-e7.
40. Brenaut E, Halvorsen JA, Dalgard FJ, Lien L, Balieva F, Sampogna F, et al. The self-assessed psychological comorbidities of prurigo in European patients: a multicentre study in 13 countries. J Eur Acad Dermatol Venereol. 2019;33(1):157-62.
41. Blome C, Beikert FC, Rustenbach SJ, Augustin M. Mapping DLQI on EQ-5D in psoriasis: transformation of skin-specific health-related quality of life into utilities. Arch Dermatol Res. 2013;305(3):197-204.
42. Steinke S, Zeidler C, Riepe C, Bruland P, Soto-Rey I, Storck M, et al. Humanistic burden of chronic pruritus in patients with inflammatory dermatoses: Results of the European Academy of Dermatology and Venereology Network on Assessment of Severity and Burden of Pruritus (PruNet) cross-sectional trial. Journal of the American Academy of Dermatology. 2018;79(3):457-63.e5.
43. Aggarwal P, Choi J, Sutaria N, Roh YS, Wongvibulsin S, Williams KA, et al. Clinical characteristics and disease burden in prurigo nodularis. Clin Exp Dermatol. 2021;46(7):1277-84.
44. Sanofi. (DoF) PN carers perspective. 2022.
45. Goulden V, Ling TC, Babakinejad P, Dawe R, Eadie E, Fassihi H, et al. British Association of Dermatologists and British Photodermatology Group guidelines for narrowband ultraviolet B phototherapy 2022. Br J Dermatol. 2022;187(3):295-308.
46. Elmariah S, Kim B, Berger T, Chisolm S, Kwatra SG, Mollanazar N, et al. Practical approaches for diagnosis and management of prurigo nodularis: United States expert panel consensus. J Am Acad Dermatol. 2021;84(3):747-60.
47. Sutaria N, Adawi W, Goldberg R, Roh YS, Choi J, Kwatra SG. Itch: Pathogenesis and treatment. J Am Acad Dermatol. 2022;86(1):17-34.
48. Williams KA, Huang AH, Belzberg M, Kwatra SG. Prurigo nodularis: Pathogenesis and management. J Am Acad Dermatol. 2020;83(6):1567-75.
49. Frølunde AS, Wiis MAK, Ben Abdallah H, Elsgaard S, Danielsen AK, Deleuran M, et al. Non-Atopic Chronic Nodular Prurigo (Prurigo Nodularis Hyde): A Systematic Review of Best-Evidenced Treatment Options. Dermatology. 2022;238(5):950-60.
50. Cameron H, Yule S, Dawe RS, Ibbotson SH, Moseley H, Ferguson J. Review of an established UK home phototherapy service 1998–2011: improving access to a cost-effective treatment for chronic skin disease. Public Health. 2014;128(4):317-24.
51. Sanofi. Data on file. Clinical study report. (Report date February 23, 2022). A randomized, double blind, placebo-controlled, multi-center, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME [EFC16459]). 2022.
52. Sanofi. Data on file. Clinical study report (Report date February 24, 2022). A randomized, double blind, placebo-controlled, multi-center, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME2 [EFC16460]). 2022.
53. Sanofi. Data on file. 2.7.3 SUMMARY OF CLINICAL EFFICACY (PRURIGO NODULARIS)- dupilumab (SAR231893/REGN668). 2022 14 March.

54. Sanofi. Data on file. 2.7.4 SUMMARY OF CLINICAL SAFETY (PRURIGO NODULARIS) - dupilumab (SAR231893/REGN668). 2022 10 March.
55. Beck LA, Deleuran M, Bissonnette R, de Bruin-Weller M, Galus R, Nakahara T, et al. Dupilumab Provides Acceptable Safety and Sustained Efficacy for up to 4 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. Am J Clin Dermatol. 2022;23(3):393-408.
56. Eichenfield LF, Bieber T, Beck LA, Simpson EL, Thaçi D, de Bruin-Weller M, et al. Infections in Dupilumab Clinical Trials in Atopic Dermatitis: A Comprehensive Pooled Analysis. Am J Clin Dermatol. 2019;20(3):443-56.
57. Wollenberg A, Beck LA, Blauvelt A, Simpson EL, Chen Z, Chen Q, et al. Assessing the need for routine safety testing for patients being treated with dupilumab for moderate-to-severe atopic dermatitis. British Journal of Dermatology. 2020;182(6):e186-e.
58. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486-96.
59. Mullol J, Laidlaw TM, Bachert C, Mannent LP, Canonica GW, Han JK, et al. Efficacy and safety of dupilumab in patients with uncontrolled severe chronic rhinosinusitis with nasal polyps and a clinical diagnosis of NSAID-ERD: Results from two randomized placebo-controlled phase 3 trials. Allergy. 2022;77(4):1231-44.
60. ClinicalTrials.gov. Study of Dupilumab for the Treatment of Patients With Prurigo Nodularis, Inadequately Controlled on Topical Prescription Therapies or When Those Therapies Are Not Advisable (PRIME2) 2022 [Available from: https://clinicaltrials.gov/ct2/show/NCT04202679.
61. Sanofi. Data on file. Amended Clinical Trial Protocol 01. A randomized, double blind, placebo-controlled, multi-center, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME2). 2020.
62. Sanofi. Data on file. Amended Clinical Trial Protocol 03. A randomized, double blind, placebo-controlled, multicenter, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME). 2021.
63. RTI Health Solutions. Date on file. Health Economic Model for Dupilumab in Prurigo Nodularis - Advisory Board Meeting Minutes (22 April 2022). 2022.
64. Sanofi. Data on file. Statistical Analysis Plan for Summary of Clinical Efficacy. 2021.
65. Sanofi. Data on file. Statistical Analysis Plan. LIBERTY-PN PRIME 2. 2021.
66. Sanofi. Data on file. Statistical Analysis Plan. LIBERTY-PN PRIME. 2021.
67. Sanofi. Data on file. ISE Appendix (28 January 2022). 2022.
68. Kwatra SG, Yosipovitch G, Ständer S, Kim BS, Msihid J, Bansal A, et al., editors. Dupilumab Improves Itch and Skin Lesions in Adults With Prurigo Nodularis Regardless of Prior Use of Immunosuppressants or Phototherapy: Post Hoc Results From the PRIME and PRIME2 Clinical Trials. Revolutionizing Atopic Dermatitis (RAD); 2022; Virtual Conference.
69. Adelphi Values. Data on file. Prurigo Nodularis Indirect Treatment Comparison Feasibility Assessment Report. 2022.

70. Goa KL. Clinical pharmacology and pharmacokinetic properties of topically applied corticosteroids. A review. Drugs. 1988;36 Suppl 5:51-61.
71. Feldweg AM, Leddy JP. Drug interactions affecting the efficacy of corticosteroid therapy a brief review with an illustrative case. J Clin Rheumatol. 1999;5(3):143-50.
72. Deleuran M, Thaçi D, Beck LA, de Bruin-Weller M, Blauvelt A, Forman S, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. J Am Acad Dermatol. 2020;82(2):377-88.
73. Lumanity. Extrapolating Post-Trial Health Outcomes in Prurigo Nodularis - Clinician Interview: Summary Report (data on file). 2022.
74. Akinlade B, Guttman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, et al. Conjunctivitis in dupilumab clinical trials. Br J Dermatol. 2019;181(3):459-73.
75. Agnihotri G, Shi K, Lio PA. A Clinician's Guide to the Recognition and Management of Dupilumab-Associated Conjunctivitis. Drugs R D. 2019;19(4):311-8.
76. Sanofi. Data on File. Periodic Benefit Risk Evaluation Report (PBRER) - 29 March 2021 to 28 March 2022. 2022.
77. Press release. Dupixent® (dupilumab) recommended for EU approval by the CHMP for the treatment of eosinophilic esophagitis. [press release]. 16 December 2022.
78. Beck LA, Thaci D, Deleuran M, Blauvelt A, Bissonnette R, de Bruin-Weller M, et al. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. Am J Clin Dermatol. 2020;21(4):567-77.
79. Halling A-S, Loft N, Silverberg JI, Guttman-Yassky E, Thyssen JP. Real-world evidence of dupilumab efficacy and risk of adverse events: A systematic review and meta-analysis. Journal of the American Academy of Dermatology. 2021;84(1):139-47.
80. Ward JR, Bernhard JD. Willan's itch and other causes of pruritus in the elderly. Int J Dermatol. 2005;44(4):267-73.
81. Rambhia PH, Levitt JO. Recalcitrant prurigo nodularis treated successfully with dupilumab. JAAD Case Rep. 2019;5(5):471-3.
82. Beck KM, Yang EJ, Sekhon S, Bhutani T, Liao W. Dupilumab Treatment for Generalized Prurigo Nodularis. JAMA Dermatol. 2019;155(1):118-20.
83. Whang KA, Le TK, Khanna R, Williams KA, Roh YS, Sutaria N, et al. Health-related quality of life and economic burden of prurigo nodularis. J Am Acad Dermatol. 2022;86(3):573-80.
84. van Os-Medendorp H, Ros WJ, Eland-de Kok PC, Kennedy C, Thio BH, van der Schuur-van der Zande A, et al. Effectiveness of the nursing programme 'Coping with itch': a randomized controlled study in adults with chronic pruritic skin disease. Br J Dermatol. 2007;156(6):1235-44.
85. Van Os-Medendorp H, Guikers CLH, Eland-de Kok PCM, Ros WJG, Bruijnzeel-Koomen CAFM, Buskens E. Costs and cost-effectiveness of the nursing programme ‘Coping with itch’ for patients with chronic pruritic skin disease. British Journal of Dermatology. 2008;158(5):1013-21.
86. Huang AH, Canner JK, Khanna R, Kang S, Kwatra SG. Real-World Prevalence of Prurigo Nodularis and Burden of Associated Diseases. J Invest Dermatol. 2020;140(2):480-3 e4.

87. National Institute for Health and Care Excellence. Baricitinib for treating moderate to severe atopic dermatitis (TA681). 2021.
88. National Institute for Health and Care Excellence. Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis (TA814). 2022.
89. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual 2022 [updated 31 January. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741.
90. Office of National Statistics (ONS). Inflation tables. 2022. Customer price inflation time series (MM23). CPIH INDEX 00: ALL ITEMS 2015=100. 2022 [Available from: https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/d7bt/mm23. .
91. Hernández Alava M, Wailoo A, Pudney S, Gray L, Manca A. Mapping clinical outcomes to generic preference-based outcome measures: development and comparison of methods. Health Technol Assess. 2020;24(34):1-68.
92. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Process and methods.; 2013.
93. University of York. Structured expert elicitation resources (STEER). 2022 [Available from: https://www.york.ac.uk/che/research/teehta/elicitation/steer/.
94. Bojke L, Soares M, Claxton K, Colson A, Fox A, Jackson C, et al. Developing a reference protocol for structured expert elicitation in health-care decision-making: a mixed-methods study. Health Technol Assess. 2021;25(37):1-124.
95. Office of National Statistics (ONS). National life tables – life expectancy in the UK: 2018 to 2020. 2021 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2018to2020.
96. Ständer S, Yosipovitch G, Legat FJ, Lacour JP, Paul C, Narbutt J, et al. Trial of Nemolizumab in Moderate-to-Severe Prurigo Nodularis. N Engl J Med. 2020;382(8):706-16.
97. Siepmann D, Lotts T, Blome C, Braeutigam M, Phan NQ, Butterfass-Bahloul T, et al. Evaluation of the antipruritic effects of topical pimecrolimus in non-atopic prurigo nodularis: Results of a randomized, hydrocortisone-controlled, double-blind phase II trial. Dermatology. 2013;227(4):353-60.
98. Tsianakas A, Zeidler C, Riepe C, Borowski M, Forner C, Gerss J, et al. Aprepitant in Anti-histamine-refractory Chronic Nodular Prurigo: A Multicentre, Randomized, Double-blind, Placebo-controlled, Cross-over, Phase-II trial (APREPRU). Acta Derm Venereol. 2019;99(4):379-85.
99. Weisshaar E, Szepietowski JC, Bernhard JD, Hait H, Legat FJ, Nattkemper L, et al. Efficacy and safety of oral nalbuphine extended release in prurigo nodularis: results of a phase 2 randomized controlled trial with an open-label extension phase. J Eur Acad Dermatol Venereol. 2022;36(3):453-61.
100. Chiricozzi A, Maurelli M, Gori N, Argenziano G, De Simone C, Calabrese G, et al. Dupilumab improves clinical manifestations, symptoms, and quality of life in adult patients with chronic nodular prurigo. Journal of the American Academy of Dermatology. 2019;83(1):39-45.
101. Napolitano M, Fabbrocini G, Scalvenzi M, Nisticò SP, Dastoli S, Patruno C. Effectiveness of Dupilumab for the Treatment of Generalized Prurigo Nodularis Phenotype of Adult Atopic Dermatitis. Dermatitis. 2020;31(1):81-4.

102. Whang K, Semenov Y, Khanna R, Williams K, Mahadevan V, Kwatra S. 723 Racial differences in the health-related quality of life of chronic pruritus patients. Journal of Investigative Dermatology. 2020;140(7):S97.
103. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.
104. Ara R, Brazier J, Zouraq IA. The Use of Health State Utility Values in Decision Models. Pharmacoeconomics. 2017;35(Suppl 1):77-88.
105. Wongvibulsin S, Sutaria N, Williams KA, Huang AH, Choi J, Roh YS, et al. A Nationwide Study of Prurigo Nodularis: Disease Burden and Healthcare Utilization in the United States. J Invest Dermatol. 2021.
106. Sutaria N, Choi J, Roh YS, Alphonse MP, Adawi W, Lai J, et al. Association of prurigo nodularis and infectious disease hospitalizations: a national cross-sectional study. Clin Exp Dermatol. 2021.
107. Nguyen M, Pona A, Ramani LT, Feldman SR, Fleischer AB. Trends in the Demographics and Treatment of Prurigo Nodularis in the United States. Journal of Cutaneous Medicine and Surgery. 2020;24(5):531-3.
108. Huang AH, Canner JK, Williams KA, Grossberg AL, Kwatra MM, Kwatra SG. Healthcare resource utilization and payer cost analysis of patients with prurigo nodularis. British Journal of Dermatology. 2020;183(1):182-4.
109. Whang KA, Kang S, Kwatra SG. Inpatient Burden of Prurigo Nodularis in the United States. Medicines. 2019;6(3):11.
110. Han J, Palomino A, Estupinan B, Wozniak A, Swan J. Psychiatric Comorbidity in Prurigo Nodularis and the Impact of Socioeconomic Status. J Clin Aesthet Dermatol. 2022;15(6):53-8.
111. Ständer S, Garbe C, Hagenström K, Petersen J, Zeidler C, Augustin M. Healthcare Utilization and Treatment Patterns in Patients with Chronic Prurigo and Chronic Pruritus in Germany. Dermatology. 2022;238(4):753-61.
112. Le TK, Whang KA, Sutaria N. 33202 Prurigo nodularis and mental health disorders among hospitalized patients in the United States. Journal of the American Academy of Dermatology. 2022;87(3, Supplement):AB97.
113. Adawi W, Sutaria N, Parthasarathy V. 35351 Association between prurigo nodularis and gastrointestinal and hepatobiliary diseases in adults: A national cross-sectional study. Journal of the American Academy of Dermatology. 2022;87(3, Supplement):AB19.
114. Sanofi. Data on file. Dupilumab for treating adults with moderate-to-severe atopic dermatitis [ID1048]. Document B. Company Evidence Submission. 2018.
115. Jones KC, Burns A. Unit costs of health and social care 2021. 2021.
116. British National Formulary (BNF). Hydrocortisone 2022 [Available from: https://bnf.nice.org.uk/drugs/hydrocortisone/medicinal-forms/#cream.
117. British National Formulary (BNF). Betamethasone (cream and ointment) 2022 [Available from: https://bnf.nice.org.uk/drugs/betamethasone/medicinal-forms/#cream.
118. British National Formulary (BNF). Clobetasone butyrate (cream and ointment) 2022 [Available from: https://bnf.nice.org.uk/drugs/clobetasone-butyrate/medicinal-forms/#cream.
119. British National Formulary (BNF). Fluocinolone acetonide (cream and ointment) 2022 [Available from: https://bnf.nice.org.uk/drugs/fluocinolone-acetonide/medicinal-forms/#cream.

120. British National Formulary (BNF). Tacrolimus 2022 [Available from: https://bnf.nice.org.uk/drugs/tacrolimus/medicinal-forms/#ointment.
121. Department of Health. NHS reference costs 2019 to 2020. 2021 [Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/.
122. British National Formulary. British National Formulary (BNF). https://bnf.nice.org.uk/. 2022.
123. Office of National Statistics (ONS). Employee earnings in the UK: 2021 2021 [Available from: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2021#employee-earnings-and-hours-worked.
124. NICE. Developing NICE guidelines: the manual. Process and methods - incorporating economic evaluation. https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation#the-reference-case. 2022.
125. Patient.info. Prurigo Nodularis: Causes, Symptoms and Treatment 2022 [Available from: https://patient.info/doctor/prurigo-nodularis-pro.
126. Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. Value Health. 2012;15(6):843-50.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dupilumab for treating prurigo nodularis

[ID4054]

Summary of Information for Patients (SIP)

File name	Version	Contains confidential information	Date
ID 4054_Dupilumab _SIP_09022023_noACIC	V 1.0	No	09 February 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Dupilumab **Brand name:** Dupixent

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adult people with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) gave a positive opinion for the use of dupilumab in adults with moderate-to-severe PN on 10th of November 2022.(1) On 17th of January 2023, the EMA authorised the label extension for dupilumab in the above population.(2) A decision from the UK regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), is expected to follow in due course. The indications currently licenced by the MHRA for dupilumab are:(3) **Atopic dermatitis** Adults and adolescents: Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. Children 6 to 11 years of age: Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy.

Asthma

Adults and adolescents: Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), see section 5.1 (of Summary of Product Characteristics), who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Children 6 to 11 years of age: Dupixent is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO) see section 5.1 (of Summary of Product Characteristics), who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Chronic rhinosinusitis with nasal polyposis (CRSwNP)
Dupixent is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Transfers of value between Sanofi UK and the relevant patient organisations in the United Kingdom are outlined below. For ease of reading, all engagements are disclosed in the format of: “Project title, amount. Disclosure statement.”

2022

Allergy UK

- Youth and Allergies – Development of Youth Engagement to create an environment for youth voice and impact, £54,000.00. Sanofi has made a financial contribution to the Youth Engagement Initiative but has had no editorial control over the content, materials or outputs.
- Financial contribution to Allergy UK *From Skin to Skin* e-booklet for Patients, £6169.00. Sanofi UK has provided a financial contribution to the production of the Skin to Skin e-booklet but has had no editorial input into the design, content or other outputs.
- Financial contribution to Allergy UK webpage The Transition Years - Dedicated area for Parents/Carers, £17,684. Sanofi UK has provided a financial contribution for development of this section for parents/carers but has had no editorial input into its design, content or any other outputs.
- Financial sponsorship of Allergy UK Respiratory Masterclass, £8452.00. Financial sponsorship of Allergy UK Respiratory Masterclass.
- Allergy UK fee for service to find and introduce a patient for a Global video project on living with atopic dermatitis, £450.00. Sanofi has paid Allergy UK a fee to find and introduce a patient for a Global video project on living with atopic dermatitis.

National Eczema Society

- Financial contribution toward National Eczema Society services 2022 – 2023, £36,000. Sanofi has provided a financial contribution to support the delivery of

National Eczema Society services in 2022-2023 and has had no editorial input into content or other outputs.
- Fee for service for National Eczema Society to introduce 3 patients to contribute to an independent report on socioeconomic costs of AD, £240.00. Sanofi UK has paid a fee to the National Eczema Society to find patients to contribute to an independent report on the socioeconomic costs of atopic dermatitis.

Eczema Outreach Support
- Eczema Outreach Support Youth Panel, £16,818.00. Sanofi UK has made a financial contribution to the Eczema Outreach Support Youth Panel but had no input into content, design, meeting logistics or other outputs of the project.

British Skin Foundation
Sanofi has supported the following projects:
- Review and help select video clips of an interview with a key opinion leader for online publication, £600.00. Sanofi UK has made a financial payment to the British Skin Foundation to review and select video clips of an interview with a key opinion leader for online publication.
- Find a patient ambassador for an ITN production, £315.00. Sanofi UK made a payment to British Skin Foundation to find a suitable patient ambassador for a Sanofi-led section of a documentary.
- BSF representative joining Sanofi Segment of ITN Productions Ages of Our Skin Documentary, £285.00. Sanofi UK has paid a fee for service to the British Skin Foundation for a representative to share BSF insights in the 'Ages of Our Skin' Sanofi ITN documentary segment. Sanofi has had no editorial input into insights provided.
- ITN Productions Ages of our Skin Documentary Sanofi Segment, £27,500. Sanofi UK has purchased an ITN Productions 'Ages of Our Skin' programme Segment reflecting a nonfinancial in-kind contribution to support British Skin Foundation involvement.
- Identifying patients with Hidradenitis Suppurativa for a Sanofi advisory board on a clinical study, £840.00. Sanofi UK has paid a fee for the British Skin Foundation patients with Hidradenitis Suppurativa for a Sanofi advisory board on a clinical study.

British Skin Foundation, Eczema Outreach Support, National Eczema Society
In addition to the above interactions, Sanofi UK has engaged National Eczema Society, Eczema Outreach Support, and the British Skin Foundation to attend a Sanofi-led workshop to develop a patient charter for people living with eczema/atopic dermatitis, £00.00. For these patient organisations, Sanofi UK discloses that it has engaged them in a zero-fee consultancy to attend a meeting to co-develop a patient charter for people with eczema/atopic dermatitis.

2021
Allergy UK
- Allergy UK to help develop and launch case studies, £2,432.00. Sanofi UK paid a fee for service to Allergy UK to help develop case studies on Atopic Dermatitis.
- Allergy UK to consult on report on costs of AD, £2911.00. Sanofi UK paid a fee for service to Allergy UK to review and comment on a report on the costs of Atopic Dermatitis.
- Allergy UK to partner on a refresh of the Seeing Red Report, £6609.00. Sanofi UK paid a fee for service to Allergy UK for their work on the update to the Seeing Red report.

- Living with allergic conditions, £33,011. Sanofi UK has provided financial support towards the creation of atopic eczema materials for patients and healthcare professionals, with no editorial input or influence.
- Digital materials on allergic rhinitis' impact on asthma, £2400.00. Sanofi UK has provided financial support towards the creation of digital materials for patients with asthma affected by allergic rhinitis with no editorial input or influence.
- VAT payment on Allergy UK Masterclass Series (payment of £14,000.00 in 2020), £2800.00. Sanofi has provided a financial contribution to co-sponsor 2 of Allergy UK's Masterclass events (2020).

National Eczema Society
National Eczema Society Corporate Membership 2021-22, £24,000.00. Sanofi UK is an industry sponsor of the National Eczema Society, supporting their work to help people living with atopic dermatitis.

Eczema Outreach Support
SGZ UK National Eczema Society Corporate Membership 2021-22, £24,000.00. Sanofi UK is an industry sponsor of the National Eczema Society, supporting their work to help people living with atopic dermatitis.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

PN is a skin disease in which people develop inflamed nodules on their skin which are usually associated with a severe itch. The nodules, if whitish or pinkish, can be surrounded by an area of darker skin. The skin is typically thickened, and the lumps may show signs of having been scratched due to the itch associated with these lumps. Symptoms such as itching can persist for many years.(4) Almost one-third of people with PN experience itchiness lasting over 10 years and another third of patients report itch lasting between one and five years.(5)

People with PN most commonly report itchiness and scratching – these symptoms can be continuous or occasional.(6) Other common symptoms include burning, stinging and tingling sensations, sleep disturbances and psychological distress.(4, 7) Less commonly reported symptoms include changes in temperature (hot and cold) and prickling, sharp, stroking or electrical sensations.(4, 7) Notably, people with PN are more likely to have anxiety and depression compared to the general population.(8)

People with PN scratch their skin repeatedly, leading to the formation of nodules which become skin lesions, as well as the development of an itch-scratch cycle that self-perpetuates.(9)
Sanofi estimates that the number of adult people in England with PN is 3.7 per 10,000 people – which equates to approximately 14,750 people.(10) Sanofi estimates that 3,953 patients of these 14,750 people with PN may not be experiencing adequate levels of symptom control with treatments applied directly to affected areas of the skin.(11)

What causes PN?
The underlying cause of PN is not completely understood. Studies suggest that PN is caused by a mix of inflammatory chemical signals and itch-causing molecules which contribute to inflammation and problems with sensation by activating immune cells.(12)

What is the impact of PN on a person's quality of life?
The impact of PN on a person's quality of life is understood to be higher than that seen in other inflammatory skin conditions.(13) While UK-specific data is limited, a study of 509 people with PN from across 12 European countries showed that:(4)

- 53% of adults with PN reported their everyday life is always or often affected.
- 38% of adults with PN reported their interaction with others is always or often affected.

A study of 52 people with PN in Denmark found that 27% of those with PN reported being more absent from work compared with their colleagues or had to retire earlier from work due to their disease.(14)

Sanofi UK interviewed a patient living with PN about what it is like to live and work with PN. They said:
"I don't go out: I hide and don't like people to see me. I have depression and anxiety: the nodular prurigo doesn't help with that because I'm anxious about people thinking about what I look like. 50 percent of my depression and anxiety is linked to nodular prurigo

because I'm anxious about going out because I don't like people looking at my skin… I work for an insurance company dealing with claims over the phone, but I wear a headset so if I have a nodule or flare on my head then it can be difficult with a headset because the pressure of it can be painful. If I'm having a flare, people can see what your face looks like via Zoom – it has an impact in that way because I know there's an issue".(15)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

People with PN can be diagnosed clinically, meaning the doctor will listen to the person describe their symptoms and then examine the affected area of their skin. To confirm this diagnosis, sometimes a skin sample is taken to be looked at under a microscope by a specialist. Under the microscope, the specialist will typically see significant thickening of the skin and marked increases of the size of nerves and nerve endings.(16)

It can often take many years for a person to be diagnosed with PN, sometimes due to a lack of awareness of the condition amongst clinicians or misdiagnosis of PN as a different disease. In 2022 Sanofi interviewed a patient living with PN who reported a 9 year delay between her symptoms starting and then her referral to a dermatologist. She added that her PN symptoms were originally attributed to another disease.(15) PN is currently understood to occur more frequently in patients over 50, and approximately half of PN patients present with a prior history of, or current atopic (allergic) diseases.(17)

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The only available licensed treatment options for PN are topical (applied directly to the skin) treatments. There are no approved, licenced systemic treatments for PN in the UK. Current treatments for PN as recommended by the International Forum for the Study of Itch in 2020 include(18) topical therapies – topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI), intralesional corticosteroids, ultraviolet (UV) phototherapy, and systemic therapies, including immunosuppressants and antidepressant treatments.

No targeted systemic treatments for PN have been licenced or approved in the UK. There is a lack of strong evidence from randomised, placebo-controlled clinical trials to support the "off-label" use (outside the approved list of treatment indications provided on the product's label) of treatments currently used for the treatment of PN. Evidence on the effectiveness of off-label treatments is mostly limited to non-randomised studies with small patient populations. **There is a variation in treatment, with no clear UK-wide guideline for the treatment of PN.**(18, 19)

Dupilumab is an effective, well-tolerated, targeted treatment that can reduce the inflammation seen in PN. The PRIME2 and PRIME clinical trials showed that dupilumab

reduced the level of itch and improved health related quality of life of people randomised to receive dupilumab. Dupilumab also provides a significantly greater reduction in associated pain at week 24; thus, it is expected to improve the health-related quality of life of people with PN, as well as the quality of life of those who care for them. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) gave a positive opinion for the use of dupilumab in adults with moderate to severe PN on the 10th of November 2022.(1) A decision from the UK regulator, the MHRA, is expected to follow in due course.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Sanofi UK interviewed a patient living with PN and the carer of the patient (partner) about living with or caring for someone with this long-term condition. The transcript representing a 3-hour interview was summarised for the person with PN and the carer, and sent back to confirm they were accurate summaries.(15, 20)

<u>Selected quotes from the summary of patient and carer can be found in italic text below:</u>

The patient living with PN

Nodular prurigo is a debilitating disease which is where you are covered in huge lumps and bumps which look a lot like spots, I've had some as big as strawberries which are huge, bright red, and itchy. I have been living with nodular prurigo for the past 13 years. The worst nodules I get are on my head and they take ages to heal – I have to shave my hair as the hair growth hurts my nodules. Sometimes your nodules will come up really quickly and erupt within a day and I've had others, for example, a huge one on my chin for 3 weeks which was incredibly painful.

If I had a magic wand, I would get rid of the pain from the nodules when they erupt and the itching. Wherever the nodule is on your body you can feel it all the time, the pain is intense, it's like sticking a hot needle in your skin. The pain isn't just associated to the lump, it can move outwards in a circle around the lump which is horrendous. If I was to rate the pain of my nodular prurigo nodules on a scale of 1-10, the nodules on my head are 8-9/10.

The next would be the itching because it's just so annoying. So that would be the two that I would love to get rid of. When the nodules are crusting over, they aren't as painful so I'd rather have those but not painful. I do take prescription painkillers for my fibromyalgia pain and that helps. Sometimes I'll use a hot compress. When the nodules have erupted it's very hard to not scratch them which makes the pain worse.

It impacts my ability to sleep if you have a particularly painful nodule. I would suggest it impacts on my sleep half the week: if I'm having a flare-up then that will impact greatly. Wherever the nodules are, you can't get comfortable, I can feel the pain and the itching, and both of those things can keep me awake. If I'm having a flare-up I will not sleep very well during the night, it will be many nodules – around 10-15 nodules with the majority on

my scalp and then my back and maybe the tops of my arms. So, it is quite a big area. It impacts on your mood because you're tired.

My diagnosis was given over the phone and 3 follow-up appointments have been cancelled due to COVID. We're two years down the line and because of COVID I've been in limbo. I find either digital or phone consultations much better because of my anxiety about going out.

The carer's testimony
The hardest bit is seeing my partner in pain – because there's nothing I can do about it, really. We've been living with nodular prurigo in various ways for the past 9 years so it's become part of our lifestyle. She (my partner) doesn't know this but it is actually quite upsetting for me when I know she's in pain and literally all I can do is go and fetch her painkillers or rub some cream in, but there's nothing physically I can do to stop the pain.(20)

The major impact, for instance I've got a concert tomorrow with the band I play with and it's now got to a point where I won't even ask her if she wants to come because I know the prurigo will stop that. The effect it has on me is that I'll have to go and do something on my own – I know she would like to join, but mentally and physically she can't.(20)

We were supposed to meet friends for a meal in and she had a prurigo flare-up the week before, so that caused the meal to be cancelled because she had a big flare-up on her head and she didn't want anyone seeing that. It frustrated me a lot because this particular set of friends live in Ireland and when they do come over it's like "Yes, yes, we must meet up"; so that probably annoyed me more than frustrated me because I wanted to go. I do a lot of other things on my own but this wasn't something that I wanted to do on my own.(20)

If I'm planning on going out, occasionally it would be very nice if she could come with me but because of her anxiety over the nodules, and the fact that she doesn't or won't leave the house can be quite frustrating... there have been occasions when I've said "come on, we'll just jump in the car and go to the seaside", or "at the weekend, we'll do this", and she will say "no, I'm having a flare-up, I don't want to go out".(20)

Those caring for people with PN may face a substantial impact on their quality of life. In 2022, Sanofi interviewed a patient with PN who said that she has to ask her carer (partner) to spend time every day applying creams to affected areas of the skin that she cannot reach herself, e.g., parts of her back:(15)

"My partner applies moisturiser to areas I can't reach, like my back. The anti-itch in the moisturiser helps some of the time. I take a prescription antihistamine at night-time on most days: my skin is nearly always itchy and it helps to reduce the itch, especially if I'm having a flare, but it doesn't make the itching go away completely. On average it's 2 hours a day, so 14 hours a week doing self-care of my nodular prurigo. If I have a big flare, I may have to spend extra time applying lotions, taking antibiotics or extra painkillers, and shaving my hair: this adds another hour a day, so, 21 hours a week."(15)

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities. If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.
PN is caused by a complicated web of chemical signals acting on immune cells and nerve cells. Two key chemical signals, called interleukin-4 and interleukin-13 (IL-4 and IL-13), are major drivers in this web and lead to increases in inflammation, itch signals and effects on the nerves in the skin.(21) Dupilumab is a recombinant human monoclonal antibody that blocks IL-4 and IL-13 from signalling.(21) Blocking the IL-4/IL-13 pathway with dupilumab decreases the inflammatory chemical signals which contribute to the underlying mechanism responsible for the long-term condition known as PN.(22) This medicine is innovative in the treatment of PN in allowing patients to administer the injection themselves at home, without needing to attend specialist centres as some patients need to with phototherapy. The medicine requires no routine monitoring, which is innovative for patients.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes/No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
UK specialist clinicians who treat PN have informed Sanofi they expect that dupilumab will be used in combination with emollients and other medicines such as topical corticosteroids and topical calcineurin inhibitors.(19) Clinical use of dupilumab for people living with PN will be refined with publication of national guidance.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Dupilumab is intended to be prescribed by all UK specialised centres. These centres currently prescribe dupilumab for conditions like atopic eczema and asthma. People who have been prescribed dupilumab for PN are recommended to receive an initial dose of 600 mg (two 300 mg injections), followed by one 300 mg injection every 2 weeks. Dupilumab is injected by the patient subcutaneously (into fatty tissue) in the thigh or abdomen using a single-use pre-filled syringe or auto-injector pen. If the injection is being given to the person with PN by someone else, the upper arm can also be used for the injection.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The clinical efficacy (how well dupilumab works) and safety of dupilumab has been studied for the treatment of PN in two main randomised trials:

- PRIME2 (NCT04202679) looked primarily at how dupilumab reduced each person's score on the Worst Itch Numeric Rating Score over 12 weeks, compared to the scores of people who had been randomly allocated to receive best supportive alone instead of dupilumab plus BSC. The study completion date was 22 November 2021.

- PRIME (NCT04183335) looked primarily at how dupilumab reduced each person's score on the Worst Itch Numeric Rating Score over 24 weeks, compared to the scores of people who had been randomly allocated to receive BSC (best supportive care) alone instead of dupilumab plus BSC. The study completion date was 3 February 2022.

Both PRIME2 and PRIME were of similar design in that they were randomised, double-blinded, controlled trials. Double blinding means that both the people enrolled in the trial and the healthcare professionals involved do not know which person has been randomised to receive either the medicine being studied, or BSC. BSC acts as a basis for comparing the effect of the medicine being studied, which is otherwise known as a control.(23) Participants randomised to the control group received BSC, defined as a combination of emollients, mild-to-moderate potency TCS (topical corticosteroids) / TCIs (topical calcineurin inhibitors) and rescue therapy.

People who could participate in PRIME2 and PRIME were adults aged 18 to 80 years who had been told they had PN by their clinicians for at least 3 months and for whom taking prescription treatments placed on the skin (e.g., steroid cream) had not helped their PN, or were unable to take prescription treatments placed on the skin.

PRIME2: The PRIME2 study was conducted at 57 centres across 11 countries/regions worldwide (Canada, Chile, France, Hungary, Italy, Portugal, Republic of Korea, Spain, Taiwan, UK and US). One trial site, which enrolled three patients, was in the UK. A total of 160 people with PN were enrolled and randomised to receive either BSC (82 people with PN) or dupilumab (78 people with PN). For further information please see Section B.2.6.2. of the submission document B.

PRIME: The PRIME study was conducted at 63 centres, across eight countries/regions worldwide (US, Argentina, Mexico, Mainland China, Japan, Russian Federation, Republic of Korea and France). A total of 151 people with PN were enrolled and randomised to receive either BSC (76 people with PN) or dupilumab (75 people with PN). For further information please see Section B.2.6.1. of the submission document B.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

When PRIME and PRIME2 were still active clinical trials, the results from PRIME2 became available while PRIME was still blinded. The results from PRIME2 showed that the treatment effect of dupilumab increased beyond 12 weeks of taking the medicine.(24)

Consequently, the study protocol for PRIME was changed to make improvement in WI-NRS≥4 (Worst Itch Numeric Rating Scale greater than or equal to 4) from start to Week 24 the primary endpoint. The original primary endpoint for PRIME – proportion of people participating in the clinical trial with improvement in WI-NRS by ≥4 from baseline to Week 12 – was changed to a secondary endpoint.
The WI-NRS is measured by marking a number between '0' (corresponding to no itch) and '10' (the worst itching imaginable). A score of 10 represents the worst itch experienced over the last 24 hours.(24)

Both PRIME2 and PRIME showed statistically significant improvement in terms of WI-NRS for people taking dupilumab compared to those receiving BSC.(24)

In the PRIME2 and PRIME studies, the primary endpoint (WI-NRS) was measured at 12 weeks and 24 weeks, respectively, with secondary endpoints being measured up to 24 weeks. This showed that patients treated with dupilumab show improvement after 12 weeks but may require a longer treatment to reach the optimal effect.(25, 26)

- **PRIME 2:** At week 12 of the PRIME2 clinical trial, 37.2% of people receiving dupilumab reported improvement (reduced score by 4 or more points) in WI-NRS compared to 22.0% of people receiving BSC alone. By week 24 of the PRIME2 clinical trial, 57.7% of people receiving dupilumab reported improvement in WI-NRS compared to 19.9% of people in the BSC group.
- **PRIME:** At week 12 of the PRIME clinical trial, 44.0% of people in the dupilumab group reported improvement in WI-NRS compared to 15.8% of people in the BSC group. At week 24 of the PRIME clinical trial, 60.0% of people in the dupilumab group reported improvement in WI-NRS compared to 18.4% of people in the BSC group.

Measuring the number of, and thickness of nodules in PRIME2 and PRIME
Clinicians involved in monitoring PRIME2 and PRIME participants were asked to give a general assessment of the participants' overall number and thickness of nodules at the start of the trials (Week 0) and Week 24. This was scored on the IGA-PN S (Investigator Global Assessment of PN scale) where clinicians rank their overall (global) impression of the severity of a person's PN based on the number and thickness of PN lesions from 0 (no lesions) to 4 (severe).

At Week 24 in both PRIME2 and PRIME, the mean IGA-PN S scores for people with PN taking dupilumab was significantly reduced compared to those receiving BSC alone.(27)

- **PRIME2:** At week 24, 44.9% of people in the dupilumab group were considered to have an IGA-PN S of 1 or 0 compared to 15.9% of people in the BSC group.
- **PRIME:** At week 24, 48.0% of people in the dupilumab group were considered to have an IGA-PN S of 1 or 0 compared to 18.4% of people in the BSC group.

The long-term effect of dupilumab has been demonstrated in an extension study in patients with moderate-to-severe AD where efficacy and health-related quality of life were observed up to 204 weeks.(28, 29) Based on this, clinical experts suggest that the benefits of dupilumab in people with moderate-to-severe PN can be assumed to extended beyond Week 24.(27, 28, 30-34)

Currently there are no ongoing studies of dupilumab for people with PN.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the PRIME2 and PRIME clinical trials, treatment with dupilumab significantly increased the health-related quality of life of people with PN participating in the trial. Health-related quality of life was measured using a questionnaire called the Dermatology Life Quality Index (DLQI).

The DLQI is a well-established 10 question questionnaire where people are asked to select on a scale of 0-3 how much their skin condition has affected specific aspects of their lives over the past week. Questions range across different topics e.g., symptoms, shopping, clothes, social activities, work, close relationships etc. Each question refers to the impact of the skin disease on the patient's life over the previous week. A total score of 30 indicates that the skin disease has had an extremely large effect on someone's quality of life, while a total score of 0 would mean that the skin disease has had no effect on someone's quality of life. In other words, the higher a person with a skin condition scores on the DLQI questionnaire, the more their quality of life is reduced.(35)

Treatment with dupilumab showed a significant decrease in DLQI score over 12 and 24 weeks compared to BSC across both clinical trials.(27)

- **PRIME2:** At week 12 there was a mean reduction in DLQI score of 12.07 in the dupilumab group compared to the BSC group which showed a mean reduction of 7.05. At week 24 there was a mean reduction in DLQI score of 13.16 in the dupilumab group compared to the BSC group which showed a mean reduction of 6.77.
- **PRIME:** At week 12 there was a mean reduction in DLQI score of 11.97 in the dupilumab group compared to the BSC group which showed a mean reduction of 5.77. At week 24, there was a mean reduction in DLQI score of 10.95 in the dupilumab group compared to the BSC group which showed a mean reduction of 5.77.

People with PN given dupilumab or receiving BSC were asked to rate the pain associated with the condition on a weekly basis from the start to Week 24 of the PRIME2 and PRIME clinical trials. The Skin Pain Numeric Rating Scale (SP-NRS) was used.(36) In the SP-NRS, people can rate the pain associated with their skin condition on a scale of 0 (no pain) to 10 (worst pain imaginable).

The individual PRIME2 and PRIME studies demonstrated the statistically significant benefit of dupilumab over BSC for the pain score SP-NRS at Week 24.(27)

- **PRIME2:** At week 24 the mean reduction in SP-NRS was 4.35 in the dupilumab group compared to the BSC group which showed a mean reduction in SP-NRS of 2.74.
- **PRIME:** At week 24 the mean reduction in SP-NRS was 4.33 in the dupilumab group compared to the BSC group which showed a mean reduction in SP-NRS of 2.16.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Dupilumab is an established treatment used in the UK since 2018. Over 500,000 patients have been treated with dupilumab for licenced indications worldwide.(37) The PRIME2 and PRIME clinical trials showed that dupilumab was well-tolerated and had an acceptable safety profile that was generally consistent with the known safety profile of dupilumab in approved indications (including eczema and asthma).(24)

Treatment-emergent serious adverse events were reported in 5 (6.7%) and 6 (8.0%) patients in dupilumab and BSC groups, respectively, in PRIME, and 2 (2.6%) and 2 (2.4%), respectively, in PRIME2. No serious adverse events were thought to be related to the intervention. Two BSC group patients (2.7%) in PRIME and 1 best BSC group patient (1.2%) in PRIME2 discontinued treatment due to a treatment-emergent adverse event; no dupilumab-treated patients discontinued treatment. Conjunctivitis occurred equally in dupilumab and BSC groups in PRIME (2 [2.7%]), however conjunctivitis was more frequent with dupilumab in PRIME2 (3 [3.9%] versus 0). None were serious or severe and none led to stopping dupilumab treatment.(24)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Systemic treatments recommended by international bodies do not have UK approval for the treatment of PN. Currently there is no approved, licenced, targeted treatment for PN in the UK. In the absence of treatments with clinical trial evidence and regulatory approval to treat PN, clinicians must rely on treatments with limited clinical trial evidence in PN. It is expected that, subject to NICE approval and guidance, any dermatologist will be able to prescribe dupilumab for people with moderate-to-severe PN.

Dupilumab provides people with PN with a treatment that will target the underlying mechanism of this long-term condition by reducing the effects of interleukin-4 and interleukin-13 – inflammatory proteins which drive inflammation associated with PN. Dupilumab was shown to reduce itch, pain, and skin lesions in two randomised, controlled trials (PRIME2 and PRIME).

People with PN can manage this long-term skin condition themselves with dupilumab without needing to visit clinics for regular blood tests as is required when they are treated with certain immunosuppressants.(2) There is no need for people with PN to attend frequent appointments required by long-term treatment of PN in for example, UV phototherapy.(38) Therefore, people with PN who are treated with dupilumab may **require fewer GP visits, hospital outpatient appointments and day case treatments compared with the use of unlicensed treatment options** such as immunosuppressants or ultraviolet phototherapy.(17, 24)

Taken together, the potential benefits of dupilumab are to reduce the resource requirements for the NHS during a period of staff shortages(39) and to reduce the burden of managing the long-term condition encountered by people with PN in attending multiple appointments for monitoring.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

People with PN may need to travel to a specialist centre for their first consultation with a dermatologist for dupilumab to be prescribed. Dupilumab has an acceptable safety profile (as noted in Section 3G) and is well tolerated across 500,000 patients worldwide across all licenced indications. Common (affecting 1 or more than 1 in 100 people) side effects associated with dupilumab may include: injection site reactions (redness, swelling, itching, pain), conjunctivitis, allergic conjunctivitis, arthralgia (joint pain), oral herpes, and eosinophilia (higher levels of a cell type – eosinophils – in the bloodstream which are often seen to be raised in allergies). These side effects may happen usually in the first 16 weeks of treatment with dupilumab.(40)

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

There is currently no approved, licenced treatment for PN in the UK. Two randomised, double-blind controlled trials have shown that dupilumab significantly reduces the level of itch as well as skin lesions compared to BSC alone.(27) Dupilumab provides the potential for cost-savings and less healthcare resource utilisation in the NHS because it reduces doctors' reliance on unlicensed, resource-intensive treatment options.(17, 38) Dupilumab thereby eases the burden across the healthcare system and delivers more economic value.

Sanofi UK heard from a group of UK clinicians with experience in treating PN. The clinicians stated that dupilumab could reduce the number of times people with PN have to be seen by a doctor in comparison to the current situation where there is no approved best supportive care for people with PN in the UK.(19)

The reduced frequency of doctors' appointments to treat and monitor people living with PN that treatment of PN with dupilumab represents would reduce the burden for both the person living with PN (taking time away from work, educational or social activities for appointments); and also reduce the burden on the healthcare system (in terms of waiting lists) by freeing up dermatologists' time to focus on other debilitating skin conditions.(41)

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

As the first and currently only therapy which targets specific chemical signals (IL-4 and IL-13) in the inflammatory pathway of PN, dupilumab represents a major step-change in the management of this condition, improving the clinical outcomes and health-related quality of life for people living with PN. The signs and symptoms of PN have a severe impact on peoples' health-related quality of life, including their emotional wellbeing. As there is currently no treatment that specifically targets the underlying mechanism of inflammation available for people living with PN, suboptimal treatment leaves them experiencing pain, itch, lost sleep and feelings of anxiety, depression, and frustration.(4, 14)

People with PN struggle at work and in their social lives with concerns about their appearance leading to issues with self-esteem and body confidence.(4, 14) Section 2a of this document contains the testimony of a patient in relation to the impact of PN on their work and social lives.(15) Dupilumab treatment for people with PN, by virtue of the significant reductions in nodules, pain and itching observed in PRIME2 and PRIME,(27) may enable them to confidently attend work (in person and/or through virtual teleconferencing platforms) and leave the house to participate in social activities, thereby improving their satisfaction with life, economic situation and future earning potential.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

People with low self-esteem or body confidence associated with their PN may be deterred from attending in-person training or educational activities as well as seeking employment in roles that require attendance at a physical workplace. The introduction of dupilumab would enable people with PN to attend training, education and attend physical workplaces, alleviating this inequity.

A study conducted in the USA looked at the characteristics of people aged 18 years old and over specific hospital who had been diagnosed with PN between 2012 and 2017. The number of people diagnosed with PN during this 5-year period was 909. The study found that African American patients were 3.4 times more likely to have PN compared to people

of White heritage.(42) The data points to a disproportionate prevalence of PN in people with non-white skin, however it is important to note that this study focused on one hospital system(42) and further studies are needed to fully characterise the prevalence of PN across people with different heritages.

Stakeholders have raised the issue that tools used to assess the severity of skin conditions may not necessarily capture the appearance of skin conditions on non-white skin, but it was also noted that the severity rating scales/tools used in PRIME2 and PRIME to evaluate dupilumab did not include the measure of "skin redness".(43) Further insights from key stakeholders on the equality considerations associated with PN can be found in the NICE Equality Impact Scoping document.(43)

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

- PRIME2 – Study of Dupilumab for the Treatment of Patients With PN, Inadequately Controlled on Topical Prescription Therapies or When Those Therapies Are Not Advisable (PRIME2). Available at: https://clinicaltrials.gov/ct2/show/NCT04202679.
- PRIME – Study of Dupilumab for the Treatment of Patients With PN, Inadequately Controlled on Topical Prescription Therapies or When Those Therapies Are Not Advisable (LIBERTY-PN PRIME) Available at: https://clinicaltrials.gov/ct2/show/NCT04183335.

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adverse event/Side effect: An unexpected medical problem that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe.

Best supportive care: a control arm in a clinical trial used as a basis to compare a new treatment against.
Clinical trial: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study.
DLQI (Dermatology Quality of Life Index): A questionnaire used to see how someone's quality of life is affected by the skin condition they live with.
EMA (European Medicines Agency): The regulatory body that evaluates, approves, and supervises medicines throughout the European Union.
HTA (Health Technology Assessment) (bodies): Bodies that make recommendations groups regarding the financing and reimbursing of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared to existing ones.
IGA-PN S (Investigator's Global Assessment for Prurigo Nodularis): A 0–4 point scoring system to assess the severity of PN based on the number and thickness of PN lesions from 0 (no lesions) to 4 (severe).
Interleukin – a type of chemical signal produced by white blood cells which helps to regulate the response of the immune system.
MHRA (Medicines and Healthcare products Regulatory Agency): The body that regulates medicines, medical devices and blood components for transfusion in the UK.
Primary Endpoint: The outcome measured to answer the key question in a clinical trial.
Quality of life: The overall enjoyment of life. Many clinical trials assess it to measure aspects of an individual's sense of wellbeing and ability to carry out activities of daily living.
Secondary Endpoint: An outcome measured to answer an additional question of interest in a clinical trial.
SP-NRS (Skin Pain Numeric Rating Scale): A 0-10 point scoring system used to establish the level of pain someone is experiencing compared to no pain (0) or the worst possible pain imaginable.(10)
WI-NRS (Worst Itch Numeric Rating Scale): A 0-10 point scoring system where score of 10 represents the worst itch experienced over the last 24 hours.(23)

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. European Medicines Agency. CHMP summary of opinion (post-authorisation) - 10 November 2022. 2022 [Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-dupixent-ii-63_en.pdf.
2. Sanofi. Summary of Product Characteristics (Dupixent). https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf. 2023.
3. EMC. Dupixent 300 mg solution for injection in pre-filled syringe - SmPC 2023 [Available from: https://www.medicines.org.uk/emc/product/8553/smpc.
4. Pereira MP, Hoffmann V, Weisshaar E, Wallengren J, Halvorsen JA, Garcovich S, et al. Chronic nodular prurigo: clinical profile and burden. A European cross-sectional study. Journal of the European Academy of Dermatology and Venereology. 2020.
5. Aggarwal P, Choi J, Sutaria N, Roh YS, Wongvibulsin S, Williams KA, et al. Clinical characteristics and disease burden in prurigo nodularis. Clin Exp Dermatol. 2021;46(7):1277-84.
6. Iking A, Grundmann S, Chatzigeorgakidis E, Phan NQ, Klein D, Stander S. Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. J Eur Acad Dermatol Venereol. 2013;27(5):550-7.

7. Zeidler C, Pereira MP, Ständer S. Chronic Prurigo: Similar Clinical Profile and Burden Across Clinical Phenotypes. Front Med (Lausanne). 2021;8:649332.
8. Brenaut E, Halvorsen JA, Dalgard FJ, Lien L, Balieva F, Sampogna F, et al. The self-assessed psychological comorbidities of prurigo in European patients: a multicentre study in 13 countries. J Eur Acad Dermatol Venereol. 2019;33(1):157-62.
9. Zeidler C, Tsianakas A, Pereira M, Stander H, Yosipovitch G, Stander S. Chronic Prurigo of Nodular Type: A Review. Acta Derm Venereol. 2018;98(2):173-9.
10. Morgan CL, Thomas M, Ständer S, Jabbar-Lopez ZK, Piketty C, Gabriel S, et al. Epidemiology of prurigo nodularis in England: a retrospective database analysis. Br J Dermatol. 2022.
11. Sanofi. Dupixent (dupilumab). Patient Funnels. 2022.
12. Kowalski EH, Kneiber D, Valdebran M, Patel U, Amber KT. Treatment-resistant prurigo nodularis: challenges and solutions. Clin Cosmet Investig Dermatol. 2019;12:163-72.
13. Steinke S, Zeidler C, Riepe C, Bruland P, Soto-Rey I, Storck M, et al. Humanistic burden of chronic pruritus in patients with inflammatory dermatoses: Results of the European Academy of Dermatology and Venereology Network on Assessment of Severity and Burden of Pruritus (PruNet) cross-sectional trial. Journal of the American Academy of Dermatology. 2018;79(3):457-63.e5.
14. Todberg T, Zachariae C, Skov L. Treatment and burden of disease in a cohort of patients with prurigo nodularis: A survey-based study. Acta Dermato-Venereologica. 2020;100(8):1-5.
15. Sanofi. Data on file. Prurigo nodularis case study - Jude's story. 2022.
16. Pereira MP, Steinke S, Zeidler C, Forner C, Riepe C, Augustin M, et al. European academy of dermatology and venereology European prurigo project: expert consensus on the definition, classification and terminology of chronic prurigo. J Eur Acad Dermatol Venereol. 2018;32(7):1059-65.
17. Zeidler C, Yosipovitch G, Stander S. Prurigo Nodularis and Its Management. Dermatol Clin. 2018;36(3):189-97.
18. Stander HF, Elmariah S, Zeidler C, Spellman M, Stander S. Diagnostic and treatment algorithm for chronic nodular prurigo. J Am Acad Dermatol. 2020;82(2):460-8.
19. Sanofi. Data on file. Advisory Board Notes (12 December 2022). 2022.
20. Sanofi. (DoF) PN carers perspective. 2022.
21. Harb H, Chatila TA. Mechanisms of Dupilumab. Clin Exp Allergy. 2020;50(1):5-14.
22. Leis M, Fleming P, Lynde CW. Prurigo Nodularis: Review and Emerging Treatments. Skin Therapy Lett. 2021;26(3):5-8.
23. National Research Council (US). Appendix A, Clinical Trials: Overview and Terminology. The Prevention and Treatment of Missing Data in Clinical Trials. Washington (DC): National Academies Press (US); 2010.
24. Sanofi. Data on file. 2.7.4 SUMMARY OF CLINICAL SAFETY (PRURIGO NODULARIS) - dupilumab (SAR231893/REGN668). 2022 10 March.
25. Sanofi. Data on file. Clinical study report. (Report date February 23, 2022). A randomized, double blind, placebo-controlled, multi-center, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME [EFC16459]). 2022.
26. Sanofi. Data on file. Clinical study report (Report date February 24, 2022). A randomized, double blind, placebo-controlled, multi-center, parallel group study to evaluate the efficacy and safety of dupilumab in patients with prurigo nodularis who are inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME2 [EFC16460]). 2022.
27. Sanofi. Data on file. 2.7.3 SUMMARY OF CLINICAL EFFICACY (PRURIGO NODULARIS)- dupilumab (SAR231893/REGN668). 2022 14 March.

28. Beck LA, Deleuran M, Bissonnette R, de Bruin-Weller M, Galus R, Nakahara T, et al. Dupilumab Provides Acceptable Safety and Sustained Efficacy for up to 4 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. Am J Clin Dermatol. 2022;23(3):393-408.
29. Deleuran M, Thaçi D, Beck LA, de Bruin-Weller M, Blauvelt A, Forman S, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. J Am Acad Dermatol. 2020;82(2):377-88.
30. Eichenfield LF, Bieber T, Beck LA, Simpson EL, Thaçi D, de Bruin-Weller M, et al. Infections in Dupilumab Clinical Trials in Atopic Dermatitis: A Comprehensive Pooled Analysis. Am J Clin Dermatol. 2019;20(3):443-56.
31. Wollenberg A, Beck LA, Blauvelt A, Simpson EL, Chen Z, Chen Q, et al. Assessing the need for routine safety testing for patients being treated with dupilumab for moderate-to-severe atopic dermatitis. British Journal of Dermatology. 2020;182(6):e186-e.
32. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486-96.
33. Mullol J, Laidlaw TM, Bachert C, Mannent LP, Canonica GW, Han JK, et al. Efficacy and safety of dupilumab in patients with uncontrolled severe chronic rhinosinusitis with nasal polyps and a clinical diagnosis of NSAID-ERD: Results from two randomized placebo-controlled phase 3 trials. Allergy. 2022;77(4):1231-44.
34. Lumanity. Extrapolating Post-Trial Health Outcomes in Prurigo Nodularis - Clinician Interview: Summary Report (data on file). 2022.
35. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-6.
36. Humphrey L, Symonds T, Gable JC, Abetz-Webb L, Silverberg JI, Griffiths P, et al. Validity and Interpretation of A Skin Pain Numeric Rating Scale Among Adults and Adolescents With Atopic Dermatitis. Value in Health. 2017;20.
37. Press release. Dupixent® (dupilumab) recommended for EU approval by the CHMP for the treatment of eosinophilic esophagitis. [press release]. 16 December 2022.
38. Franken SM, Vierstra CL, Rustemeyer T. Improving access to home phototherapy for patients with psoriasis: current challenges and future prospects. Psoriasis (Auckl). 2016;6:55-64.
39. Levell N. Dermatology GIRFT Programme National Specialty Report. 2021 [Available from: https://www.gettingitrightfirsttime.co.uk/wp-content/uploads/2022/07/DermatologyReport-Sept21o.pdf.
40. National Institute for Health and Care Excellence. Dupilumab for treating moderate to severe atopic dermatitis (TA534). 2018.
41. Hudson RDA, Ameen M, George SMC, Harwood CA, Weller RB, Lear JT, et al. A Real-World Data Study on the Healthcare Resource Use for Uncontrolled Moderate-to-Severe Atopic Dermatitis in Secondary Care in the United Kingdom Prior to the Introduction of Biologic Treatment. Clinicoecon Outcomes Res. 2022;14:167-77.
42. Boozalis E, Tang O, Patel S, Semenov YR, Pereira MP, Stander S, et al. Ethnic differences and comorbidities of 909 prurigo nodularis patients. Journal of the American Academy of Dermatology. 2018;79(4):714-9.e3.
43. National Institute for Health and Care Excellence. Equality impact assessment – Scoping. Dupilumab for treating moderate to severe prurigo nodularis [ID4054] 2022 [Available from: https://www.nice.org.uk/guidance/gid-ta11081/documents/equality-impact-assessment-scoping.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Dupilumab for treating prurigo nodularis

Clarification questions

March 2023

File name	Version	Contains confidential information	Date
ID4054 Dupilumab for prurigo nodularis EAG Clarification_company response_corrected_29032023_fully redacted	V2	No	29/03/2023

Notes for company

Highlighting in the template

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

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Additional information required

A1. Priority Question: Some of the hyperlinks in the PRIME2 and PRIME CSRs do not work e.g., "16-2-1-disposition [16.2.1.3]" on p30 of the PRIME 2 CSR. Please provide new versions of the CSRs where all the hyperlinks work.

The hyperlinks in the CSR body text supplied refer to data tables and figures in appendices to the CSR. These documents are many thousands of pages long and in some cases contain individual patient data (anonymised). In order for the links to work the CSR body must be connected to the data tables and figures.

We are happy to provide any tables or figures from the CSR body text identified by the EAG for the purposes of this submission however we believe that linkage and provision of the full appendices would not be an efficient use of resource. The document identified in the hyperlink 16.2.1.3 is now provided in the supporting materials to this response, as Appendix 9. Please let us know if further information identified in hyperlinks is required.

A2. Priority Question: Please provide the following references:

(1) Reference 1. Sanofi. Data on file. Advisory Board Notes (12 December 2022). 2022.

(2) Reference 63. RTI Health Solutions. Date on file. Health Economic Model for Dupilumab in Prurigo Nodularis - Advisory Board Meeting Minutes (22 April 2022). 2022.

The requested references are now provided as Appendices to the submission. Please see Appendix 10 and Appendix 11 as attachments to our response document.

Decision problem

A3. Please provide further justification for excluding disease-free period/maintenance of remission and time to relapse/prevention of relapse outcomes.

The clinical trials were not designed or powered sufficiently to provide results for the above outcomes.

Systematic review

A4. Appendix D Table 12 (Table 1 in this document) presents the list of excluded studies from the clinical SLR, please provide further justification for the exclusion of the following studies, which appear to meet inclusion criteria:

Table 1. Excluded studies in clinical SLR

First author and year	Reason for exclusion	EAG comment	Response
Pereira, 2021	Outcomes not of interest	Inclusion criteria states 'any PROs' therefore this study appears to meet inclusion criteria	This study is a review of clinical burden and QoL of chronic nodular prurigo and therefore had no intervention. Exclusion reason should be revised to "No intervention"
Bergquist, 2021	Study design not of interest	Case series ≤5 cases were excluded, this study is a case series of 6 patients	This was excluded as it is a letter to the editor

Grundel, 2020	Study design not of interest	Retrospective studies were eligible for inclusion, this is a retrospective study of 325 patients	This study is retrospective study examining the treatment burden between chronic nodular prurigo and chronic pruritus. Exclusion reason should be revised to "No intervention"
Georgakopoulos, 2021	Study design not of interest	Retrospective studies were eligible for inclusion, this is a retrospective study of 19 patients treated with dupilumab	This reference was excluded because it is a letter to the editor

PRIME2/PRIME trials

A5. Priority Question: Please provide details of the number of patients in each treatment arm of PRIME2 and PRIME who were still being treated and had completed the post-treatment follow-up period for each of the analyses at the different timepoints (i.e. week 4, week 8, week 12 and week 24 in Table 12 and at each week in Figures 7-11 and 13).

The requested analysis is now provided as an Appendix to our response document. Please see Appendix 1 as attachment.

The following analyses are provided in response to question A5 in the Appendix:

- Time to first treatment discontinuation during planned treatment period
- Pooled ITT population among patients who completed the study period
- Pooled ITT population among patients who did not complete the study period
- ITT population from EFC16459 who completed the study period
- ITT population from EFC16459 who did not complete the study period
- ITT population from EFC16460 who completed the study period
- ITT population from EFC16460 who did not complete the study period

A6. Priority Question: Please provide more complete data, if available, since the primary cut-off dates for PRIME2 and PRIME were 30/8/21 and 12/11/21, respectively.

A more detailed data set has been provided during the submission with the addition of pooled efficacy and safety analysis, in response to questions A10 and A12. In addition, we have provided updated pooled safety analysis in other section of this response (data updates from March 2022).

A7. Priority Question: Please provide details of the rescue treatments or prohibited medications/procedures given to patients who were considered non-responders, but included in the as-observed supplementary analyses and patients included in the safety population.

A summary of prohibited medication/procedure is provided in.Table 2, with greater details of the prohibited topical and systemic agents used in subsequent tables. Please see more detailed information in Appendix 3.

Table 2. Summary of concomitant prohibited medications/procedures. Pooled PRIME2/PRIME:

Pooled from PRIME2/PRIME	Placebo (n=158)	Dupilumab (n=153)
Any prohibited medications/procedures and/or rescue medications	[redacted]	[redacted]
Prohibited medications	[redacted]	[redacted]
Prohibited procedures	[redacted]	[redacted]
Rescue medications	[redacted]	[redacted]

Table 3. Concomitant rescue medications.

Standardised medication, n (%)	Placebo (n=158)	Dupilumab (n=153)
Any concomitant prohibited medication	[redacted]	[redacted]
Systemic immunosuppressive/immunomodulator drugs	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]
Ciclosporin	[redacted]	[redacted]
Hydroxychloroquine sulfate	[redacted]	[redacted]
Meprednisone	[redacted]	[redacted]

Methotrexate	[redacted]	[redacted]
Methylprednisolone	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]
Thalidomide	[redacted]	[redacted]
Triamcinolone acetonide	[redacted]	[redacted]
Tripterygium spp. Total glycoside extract	[redacted]	[redacted]
Tripterygium wilfordii glycoside extract	[redacted]	[redacted]
Other monoclonal antibodies (that are biologic modifiers)	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]
Naltrexone or other opioid antagonist	[redacted]	[redacted]
Tramadol hydrochloride	[redacted]	[redacted]
Paracetamol; tramadol hydrochloride	[redacted]	[redacted]
Tapentadol hydrochloride	[redacted]	[redacted]
Gabapentin and pregabalin	[redacted]	[redacted]
Thalidomide	[redacted]	[redacted]
• Thalidomide	[redacted]	[redacted]
Paroxetine, fluvoxamine, or other SSRIs	[redacted]	[redacted]
SNRIs	[redacted]	[redacted]
Tramadol hydrochloride	[redacted]	[redacted]
Dextromethorphan hydrobromide	[redacted]	[redacted]
Dextromethorphan hydrobromide; guaifenesin	[redacted]	[redacted]
Paracetamol; tramadol hydrochloride	[redacted]	[redacted]
Amitriptyline or other tricyclic or tetracyclic and depressants	[redacted]	[redacted]
• Amitriptyline hydrochloride	[redacted]	[redacted]
Sedating antihistamine	[redacted]	[redacted]
Non-sedating antihistamine if used specifically for the treatment of itch secondary to AD or PN	[redacted]	[redacted]
Fexofenadine hydrochloride	[redacted]	[redacted]
Levocetirizine dihydrochloride	[redacted]	[redacted]

Standardised medication, n (%)	**Placebo (n=158)**	**Dupilumab(n=153)**
TCI used for rescue	[redacted]	[redacted]
• **Tacrolimus**	[redacted]	[redacted]

• **Tacrolimus monohydrate**	[redacted]	[redacted]

Table 4. Summary of any concomitant prohibited medication.

Standardised medication, n (%)	**Placebo (n=158)**	**Dupilumab (n=153)**
Any concomitant prohibited medication	[redacted]	[redacted]
Systemic immunosuppressive/immunomodulator drugs	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]
Ciclosporin	[redacted]	[redacted]
Hydroxychloroquine sulfate	[redacted]	[redacted]
Meprednisone	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]
Methylprednisolone	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]
Thalidomide	[redacted]	[redacted]
Triamcinolone acetonide	[redacted]	[redacted]
Tripterygium spp. Total glycoside extract	[redacted]	[redacted]
Tripterygium wilfordii glycoside extract	[redacted]	[redacted]
Other monoclonal antibodies (that are biologic modifiers)	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]

Naltrexone or other opioid antagonist	[redacted]	[redacted]
Tramadol hydrochloride	[redacted]	[redacted]
Paracetamol; tramadol hydrochloride	[redacted]	[redacted]
Tapentadol hydrochloride	[redacted]	[redacted]
Gabapentin and pregabalin	[redacted]	[redacted]
Thalidomide	[redacted]	[redacted]
• **Thalidomide**	[redacted]	[redacted]
Paroxetine, fluvoxamine, or other SSRIs	[redacted]	[redacted]
SNRIs	[redacted]	[redacted]
Tramadol hydrochloride	[redacted]	[redacted]
Dextromethorphan hydrobromide	[redacted]	[redacted]
Dextromethorphan hydrobromide; guaifenesin	[redacted]	[redacted]
Paracetamol; tramadol hydrochloride	[redacted]	[redacted]
Amitriptyline or other tricyclic or tetracyclic and depressants	[redacted]	[redacted]
• **Amitriptyline hydrochloride**	[redacted]	[redacted]
Sedating antihistamine	[redacted]	[redacted]
Non-sedating antihistamine if used specifically for the treatment of itch secondary to AD or PN	[redacted]	[redacted]
Fexofenadine hydrochloride	[redacted]	[redacted]
Levocetirizine dihydrochloride	[redacted]	[redacted]

Table 5. Detailed summary of concomitant prohibited procedures.

Procedures, n (%)	Placebo (n=158)	Dupilumab (n=153)
Any concomitant prohibited procedure	[redacted]	[redacted]
Cryotherapy	[redacted]	[redacted]
• Surgical and medical procedures	[redacted]	[redacted]
• HLT: Therapeutic procedures NEC	[redacted]	[redacted]
• PT: Cryotherapy	[redacted]	[redacted]
Intralesional corticosteroid injections	[redacted]	[redacted]
• Surgical and medical procedures	[redacted]	[redacted]
○ HLT: Therapeutic procedure NEC	[redacted]	[redacted]
○ PT: Injection	[redacted]	[redacted]

A8. Priority Question: Please provide details of all best supportive care used by patients in each treatment arm of PRIME2 and PRIME, including numbers of patients receiving each treatment in each treatment arm.

All participants received at least one concomitant medication during the study. The concomitant medications taken by the highest number of participants in either dupilumab or placebo groups by standardized medication name were emollients and protectives ([redacted] and [redacted]), mometasone furoate ([redacted] and [redacted]), tozinameran ([redacted] and [redacted]), acetylsalicylic acid ([redacted] and [redacted]), and paracetamol ([redacted] and [redacted]). See detailed tables below for a full list and percentages of patients on these therapies in Appendix 12.

A9. Please provide results for other efficacy outcomes listed in Table 4 which are not reported in the clinical effectiveness section of the submission, i.e. EQ-5D-5L, EQ-5D VAS, PGIC, PGIS.

Please see summary table provided for question A13 in Appendix 7. The table contains missing outcomes listed in question A9.

A10. Priority Question: Please provide results at week 36 (EOS) after the 12-week post-treatment follow-up period for each treatment arm of PRIME2 and PRIME, to give an indication of loss of response after treatment withdrawal.

The requested analysis is now provided as Appendix to the submission. Please see Appendix 1 as attachment to our response document.

The following analyses are provided in response to question A10 in the Appendix:

- Proportion of participants with WI-NRS improvement (reduction) ≥ 4 points from baseline at week 36 according to the response at week 24 (primary method)
    - Pooled ITT population
    - ITT population from EFC16459
    - ITT population from EFC16460
- Proportion of participants with IGA PN-S score 0 or 1 at week 36 according to the response at week 24 (primary method)
    - Pooled ITT population
    - ITT population from EFC16459
    - ITT population from EFC16460
- Proportion of participants with both WI-NRS improvement (reduction) ≥ 4 points from baseline at week 36 and IGA PN-S score 0 or 1 at week 36 according to the response at week 24 (primary method)
    - Pooled ITT population
    - ITT population from EFC16459
    - ITT population from EFC16460

The PRIME2/PRIME trials were not designed or powered to evaluate maintenance of remission following discontinuation of study intervention between weeks 24 to 36. Furthermore, any such analysis would be hindered by the elevated numbers of patients lost to follow up due to the impact of the COVID pandemic while this trial was conducted.

A11. Please provide any available data on adherence to dupilumab/placebo and best supportive care in each treatment arm of PRIME2 and PRIME.

The safety pool comprised [redacted] randomised participants who received either dupilumab (N=[redacted]) or placebo (N=[redacted]) (Table 6). There were 2 participants who were randomised but not exposed to study intervention: for 1 participant (dupilumab group) the reason for withdrawal was not related to safety issues, and for the other participant (placebo group) the reason for withdrawal from the study was fear of being exposed to COVID-19.

[redacted] ([redacted]) of the total number of participants included in the safety pool completed the 24-week study intervention period and [redacted] ([redacted]) prematurely discontinued the study intervention prior to Week 24. The percentage of participants who discontinued the study intervention was lower in the dupilumab group ([redacted]) versus the placebo group ([redacted]). Overall, the main reasons for permanent intervention discontinuation prior to Week 24 were withdrawal by participant ([redacted] in the dupilumab group and [redacted] in the placebo group) and lack of efficacy ([redacted] in the dupilumab group and [redacted] in the placebo group). Adverse events as a reason for discontinuation were reported in [redacted] ([redacted]) participants in the placebo group and [redacted] participants in the dupilumab group.

Table 6. Participant disposition – pooled safety population.

Patient randomised to IMP, n (%)	**Placebo (n=157)**	**Dupilumab (n=152)**	**All (n=309)**
Randomised and exposed	[redacted]	[redacted]	[redacted]
Completed 24 Week study intervention	[redacted]	[redacted]	[redacted]
Did not complete the 24-week study intervention	[redacted]	[redacted]	[redacted]
Reason for permanent study intervention withdrawal prior to week 24			
• Adverse event	[redacted]	[redacted]	[redacted]
• Lack of efficacy	[redacted]	[redacted]	[redacted]

• Poor compliance to protocol	[redacted]	[redacted]	[redacted]
• Withdrawal by participant	[redacted]	[redacted]	[redacted]

Compliance to study intervention

Participants in both dupilumab and placebo groups had a high [redacted] mean injection compliance rate, with no difference observed between intervention groups.

Compliance to background intervention

Participants were required to apply moisturizers (emollients) once or twice daily for at least 5 out of 7 consecutive days immediately before Day 1 and continue until Week 36. In addition, if participants were on a stable regimen of low to medium potency TCS or TCI at screening, they could continue their topical steroid application once daily without tapering from screening to Week 24. If participants were on stable regimens of high potency or super-potent steroids at screening, they were to decrease potency to medium potency TCS and continue to apply daily from screening to Week 24.

The mean compliance to background intervention emollients was generally high throughout the studies and similar between intervention groups ([redacted] and [redacted] from baseline to Week 24 in the dupilumab and placebo participants, respectively, Table 7 below). In those participants who used stable doses of TCS/TCI, the mean compliance with TCS/TCI was also high and similar in both intervention groups ([redacted] and [redacted] from baseline to Week 24 in the dupilumab and placebo participants, respectively, Table 8 below).

Table 7. Compliance to emollients.

Background interventions emollients, baseline to Week 24	**Placebo (n=157)**	**Dupilumab (n=153)**
Mean (SD)	[redacted]	[redacted]

Table 8. Compliance to TCS/TCI.

Participants with stratification of stable use of TCS/TCI, baseline to Week 24	Placebo (n=91)	Dupilumab (n=91)
Mean (SD)	[redacted]	[redacted]

A12. Please present summary data on adverse events from RCTs of dupilumab in other indications (e.g., from systematic reviews or other pooled trial analyses). Please also include any longer-term data where available.

Please see summary document provided for question A12 in Appendix 6.

A13. Priority Question: For the PRIME2, PRIME and pooled analyses, please provide results (including the missing outcomes described in question A9) for all the supplementary analyses (as-observed, hybrid method, and tipping point) using Table 12 in Document B as a template for presenting all outcomes and results.

Please see summary table provided for question A13 in Appendix 2 and 7. The table contains data for the missing outcomes listed in question A9.

A14. In Table 10 of the CS, it states that continuous missing data after rescue treatment and treatment discontinuation were imputed using the worst-observation carried forward (WOCF) method.

a) Please explain your reasoning for selecting this method.

Given that rescue medication was available in the trial, WOCF is a suitable approach. Efficacy measurements collected after the use of rescue medication can be substantially confounded by the intercurrent events. In the absence of rescue medication a patient's disease control would likely decline to the status of worst observed, rather than the status that recorded in the LOCF method, if no rescue medication were given or after discontinuation of study treatment due to lack of efficacy.

b) Please provide results using the last observation carried forward (LOCF) method that was used in the appraisal for atopic dermatitis.

LOCF method was not planned in PRIME2/PRIME studies, therefore Sanofi doesn't have the data to provide the requested analysis.

A15. Priority Question: For the PRIME2, PRIME and pooled analyses for: WI-NRS improvement (reduction) by ≥4 points (Week 24); patients with IGA PN-S 0 or 1 (Week 24); and patients with both an improvement (reduction) in WI-NRS by ≥4 points and IGA PN-S score of 0 or 1 (Week 24), please provide details of how many patients were represented by imputed data and the reason data were missing, i.e. rescue treatment used, treatment discontinuation, etc. Please do this for the main analysis, the as-observed analysis, and the hybrid method analysis.

The requested analysis is now provided as Appendix to the submission. Please see Appendix 2 as attachment to our response document.

The following analyses are provided in response to question A15 in the Appendix:

- Proportion of participants with WI-NRS improvement (reduction) >=4 points from baseline at Week 24 - ITT population from EFC16460 and EFC16459 and Pooled ITT population
    - Primary method
    - As-observed method
    - Hybrid method - ITT population from EFC16459
    - Hybrid method - ITT population from EFC16460
    - Hybrid method - Pooled ITT population
- Proportion of participants with IGA PN-S 0 or 1 score at Week 24 - ITT population from EFC16460 and EFC16459 and Pooled ITT population
    - Primary method
    - As-observed method
    - Hybrid method - ITT population from EFC16459
    - Hybrid method - ITT population from EFC16460
    - Hybrid method - Pooled ITT population

- Proportion of participants with both an improvement (reduction) in WI-NRS by >=4 points from baseline to Week 24 and an IGA PN-S 0 or 1 score at Week 24 - ITT population from EFC16460 and EFC16459 and Pooled ITT population
    - Primary method
    - As-observed method
    - Hybrid method - ITT population from EFC16459
    - Hybrid method - ITT population from EFC16460
    - Hybrid method - Pooled ITT population

A16. In Table 11 of the CS the question “Were there any unexpected imbalances in dropouts between groups?” is answered ‘no’. This seems to contradict the imbalances reported in Table 13 of the appendices. Please discuss the possible impact of these imbalances on results for i) WI-NRS improvement ii) IGA PN-S score of 0 or 1, based on the different imputation methods used across the various methods of trial analyses.

As per the protocols and statistical analysis plans of the clinical trials, participants with missing data or those who received prohibited medications/procedures and/or rescue medications impacting efficacy were imputed as non-responders. Missing data are therefore not the only reason that a participant might be imputed as a non-responder. Table 9 summarises reasons for imputation of non-responders in both studies. Use of prohibited/rescue medication was the most frequent reason and higher in placebo in both studies at both timepoints. Data of participants taking the prohibited/rescue medication were set to missing after the medication usage and participants were imputed as non-responders in WI-NRS and IGA PN-S analyses. Other participants who were imputed as WI-NRS and IGA PN-S non-responders had mainly missing data due to premature discontinuation of study. They discontinued the study intervention due to lack of efficacy, AE or other reason and did not continue with the remaining study visits as suggested in the study protocols.

Table 9. Summary of number of participants with WI-NRS or IGA PN-S data imputed as non-responders in the primary/key secondary analysis.

			EFC16460		EFC16459	
Visit	**Parameter**	**Reason for imputation***	**Placebo (N=82)**	**Dupilumab 300 mg Q2W (N=78)**	**Placebo (N=76)**	**Dupilumab 300 mg Q2W (N=75)**
Week 12	WI-NRS		[redacted]	[redacted]	[redacted]	[redacted]
		Prohibited/rescue medication	[redacted]	[redacted]	[redacted]	[redacted]
		Discontinuation due to lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
		Discontinuation due to AE	[redacted]	[redacted]	[redacted]	[redacted]
		Discontinuation due to other reason	[redacted]	[redacted]	[redacted]	[redacted]
		Treatment completed but with missing data#	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	WI-NRS		[redacted]	[redacted]	[redacted]	[redacted]
		Prohibited/rescue medication	[redacted]	[redacted]	[redacted]	[redacted]
		Discontinuation due to lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
		Discontinuation due to AE	[redacted]	[redacted]	[redacted]	[redacted]
		Discontinuation due to other reason	[redacted]	[redacted]	[redacted]	[redacted]
		Treatment completed but with missing data#	[redacted]	[redacted]	[redacted]	[redacted]
	IGA PN-S		[redacted]	[redacted]	[redacted]	[redacted]
		Prohibited/rescue medication	[redacted]	[redacted]	[redacted]	[redacted]
		Discontinuation due to lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
		Discontinuation due to AE	[redacted]	[redacted]	[redacted]	[redacted]
		Discontinuation due to other reason	[redacted]	[redacted]	[redacted]	[redacted]
		Treatment completed but with missing data#	[redacted]	[redacted]	[redacted]	[redacted]

* Patients with multiple reasons were classified first as 'Prohibited/rescue medication', then 'Discontinuation due to lack of efficacy', and then 'Discontinuation due to AE'.
# including 1 untreated dupilumab participant from EFC16460 and 1 untreated placebo participant from EFC16459

The discontinuations for other reason were related to withdrawal by subject, as displayed in Table 10. Of note, in participants who discontinued the study intervention but

continued with the remaining study visits, their post-discontinuation data were included in the analyses.

Table 10. Permanent study intervention discontinuations due to withdrawal by subject

Reason for permanent study intervention discontinuation		EFC16460		EFC16459	
		Placebo (N=82)	Dupilumab 300 mg q2w (N=78)	Placebo (N=76)	Dupilumab 300 mg q2w (N=75)
Withdrawal by subject	Reason: Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
	Reason: Other	[redacted]	[redacted]	[redacted]	[redacted]

Table 11, Table 12, Table 13 and Table 14 presented below show WI-NRS and IGA PN-S response results of PRIME and PRIME2 at Week 12 and Week 24. In both studies, data show a higher number of imputed non-responders in the placebo group at Week 12 and Week 24.

Table 11. Proportion of participants with an improvement (reduction) in WI-NRS by >=4 points from baseline at Week 24 - ITT population from EFC16460 and EFC16459 and Pooled ITT population.

		EFC16460		EFC16459		Pooled Data
	Placebo	Dupilumab 300 mg	Placebo	Dupilumab 300 mg	Placebo	Dupilumab 300 mg
	(N=82)	Q2W	(N=76)	Q2W	(N=158)	Q2W
	n (%)	(N=78) n (%)	n (%)	(N=75) n (%)	n (%)	(N=153) n (%)
Weekly average WI-NRS improvement ≥4 points at Week 24 from baseline						
Responder	16 (19.5)	45 (57.7)	14 (18.4)	45 (60.0)	30 (19.0)	90 (58.8)
Non-responder	66 (80.5)	33 (42.3)	62 (81.6)	30 (40.0)	128 (81.0)	63 (41.2)
Imputed non-responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR, 95% CI vs. placebo[a]		[redacted]		[redacted]		[redacted]
P-value vs. placebo[b]		[redacted]		[redacted]		[redacted]
RRD (%), 95% CI vs. placebo[a]		[redacted]		[redacted]		[redacted]

CMH: Cochran-Mantel Haenszel; WI-NRS: worst-itch numeric rating scale; CI: confidence interval; TCS: topical corticosteroids; TCI: topical calcineurin inhibitors.

a OR: odds ratio; RRD: response rate difference; derived from the Mantel-Haenszel estimator.

b CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no). In addition, the pooled analysis was also adjusted by study indicator (EFC16459 or EFC16460).

Note: Participants who received the prohibited medications/procedures and/or rescue medications that impacted efficacy before Week 24 were considered as non-responders, and participants with missing data at Week 24 were considered as non-responders.

Table 12. Proportion of participants with WI-NRS improvement (reduction) >=4 points from baseline at Week 12 - ITT population from EFC16460 and EFC16459 and Pooled ITT population.

		EFC16460		EFC16459		Pooled Data
	Placebo	Dupilumab 300 mg	Placebo	Dupilumab 300 mg	Placebo	Dupilumab 300 mg
	(N=82)	Q2W	(N=76)	Q2W	(N=158)	Q2W
	n (%)	(N=78) n (%)	n (%)	(N=75) n (%)	n (%)	(N=153) n (%)
Weekly average WI-NRS improvement ≥4 points at Week 12 from baseline						
Responder	18 (22.0)	29 (37.2)	12 (15.8)	33 (44.0)	30 (19.0)	62 (40.5)
Non-responder	64 (78.0)	49 (62.8)	64 (84.2)	42 (56.0)	128 (81.0)	91 (59.5)
Imputed non-responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR, 95% CI vs. placebo[a]		[redacted]		[redacted]		[redacted]
P-value vs. placebo[b]		[redacted]		[redacted]		[redacted]
RRD (%), 95% CI vs. placebo[a]		[redacted]		[redacted]		[redacted]

CMH: Cochran-Mantel Haenszel; WI-NRS: worst-itch numeric rating scale; CI: confidence interval. TCS: topical corticosteroids; TCI: topical calcineurin inhibitors.

a OR: odds ratio; RRD: response rate difference; derived from the Mantel-Haenszel estimator.

b CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no). In addition, the pooled analysis was also adjusted by study indicator (EFC16459 or EFC16460).

Note: Participants who received the prohibited medications/procedures and/or rescue medications that impacted efficacy before Week 12 were considered as non-responders, and participants with missing data at Week 12 were considered as non-responders.

Table 13. Proportion of participants with IGA PN-S 0 or 1 score at Week 24 - ITT population from EFC16460 and EFC16459 and Pooled ITT population.

		EFC16460		EFC16459		Pooled Data
	Placebo	Dupilumab 300 mg	Placebo	Dupilumab 300 mg	Placebo	Dupilumab 300 mg

	(N=82)	Q2W	(N=76)	Q2W	(N=158)	Q2W
	n (%)	(N=78) n (%)	n (%)	(N=75) n (%)	n (%)	(N=153) n (%)
IGA PN-S 0 or 1 score						
Responder	13 (15.9)	35 (44.9)	14 (18.4)	36 (48.0)	27 (17.1)	71 (46.4)
Non-responder	69 (84.1)	43 (55.1)	62 (81.6)	39 (52.0)	131 (82.9)	82 (53.6)
Imputed non-responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR, 95% CI vs. placebo[a]		[redacted]		[redacted]		[redacted]
P-value vs. placebo[b]		[redacted]		[redacted]		[redacted]
RRD (%), 95% CI vs. placebo[a]		[redacted]		[redacted]		[redacted]

CMH: Cochran-Mantel Haenszel; IGA PN-S: Investigator's Global Assessment 0 or 1 score for PN-Stage; CI: confidence interval. TCS: topical corticosteroids; TCI: topical calcineurin inhibitors.

a OR: odds ratio; RRD: response rate difference; derived from the Mantel-Haenszel estimator.

b CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no). In addition, the pooled analysis was also adjusted by study indicator (EFC16459 or EFC16460).

Note: Participants who received the prohibited medications/procedures and/or rescue medications that impacted efficacy before Week 24 were considered as non-responders, and participants with missing data at Week 24 were considered as non-responders.

Table 14. Proportion of participants with IGA PN-S 0 or 1 score at Week 12 - ITT population from EFC16460 and EFC16459 and Pooled ITT population.

		EFC16460		EFC16459		Pooled Data
	Placebo	Dupilumab 300 mg	Placebo	Dupilumab 300 mg	Placebo	Dupilumab 300 mg
	(N=82)	Q2W	(N=76)	Q2W	(N=158)	Q2W
	n (%)	(N=78) n (%)	n (%)	(N=75) n (%)	n (%)	(N=153) n (%)
IGA PN-S 0 or 1 score						
Responder	10 (12.2)	20 (25.6)	9 (11.8)	24 (32.0)	19 (12.0)	44 (28.8)
Non-responder	72 (87.8)	58 (74.4)	67 (88.2)	51 (68.0)	139 (88.0)	109 (71.2)
Imputed non-responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR, 95% CI vs. placebo[a]		[redacted]		[redacted]		[redacted]
P-value vs. placebo[b]		[redacted]		[redacted]		[redacted]
RRD (%), 95% CI vs. placebo[a]		[redacted]		[redacted]		[redacted]

CMH: Cochran-Mantel Haenszel; IGA PN-S: Investigator's Global Assessment 0 or 1 score for PN-Stage; CI: confidence interval. TCS: topical corticosteroids; TCI: topical calcineurin inhibitors.

a OR: odds ratio; RRD: response rate difference; derived from the Mantel-Haenszel estimator.

b CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region and baseline anti-depressant use (yes or no). In addition, the pooled analysis was also adjusted by study indicator (EFC16459 or EFC16460).

Note: Participants who received the prohibited medications/procedures and/or rescue medications that impacted efficacy before Week 12 were considered as non-responders, and participants with missing data at Week 12 were considered as non-responders.

Supplementary analyses for both primary and key secondary endpoints including as-observed analysis performed by including data after the use of prohibited medications/procedures and/or rescue medications, a hybrid method analysis performed by censoring the data after prohibited medications/procedures and/or rescue medications and thereafter using a hybrid data imputation approach, and a tipping point analysis using MIs for missing data were consistent with that from the primary analysis for both studies PRIME and PRIME2.

In summary, in PRIME and PRIME2 the higher number of imputed non-responders in the placebo group at Week 12 and Week 24 was mostly driven by use of prohibited/rescue medication and study discontinuation. Only a few patients who completed the study had missing data. The higher rate of imputed data (with or without missing data) in the placebo group is likely to be explained by the expected higher risk of uncontrolled disease in this group, leading to the need for rescue treatment and/or to study discontinuation.

A17. Please comment on the applicability (to the NHS) of the best supportive care interventions given to patients in the PRIME trials, paying particular attention to the use of systemic treatments, such as methotrexate, in current NHS practice in this patient population.

Best supportive care in the PRIME2/PRIME studies included emollients in all patients and mild-moderate potency topical steroids in some patients. These are broadly applicable to the NHS, although in the NHS topical steroids are usually high potency or else high potency under occlusion. A number of reports have highlighted the burden of such treatment regimens on QoL and the level of compliance associated with this regime for long-term control.

Methotrexate was a prohibited medication in the PRIME trials. Despite a lack of evidence for their efficacy in PN, methotrexate is used off-label in clinical practice (see Sanofi advisory board report December 2022). A pan-European physician consensus statement, including physicians from the UK, reported that immunosuppressant was effective in less than 27% of patients with prurigo nodularis (Pereira MP et al 2018). Moreover, the clinical experts highlighted that conventional

systemics are not appropriate in a number of PN patients due to concomitant comorbidities and the level of polypharmacy in a significant portion of these patients, especially those of advanced years.

Comparison between PRIME2 and PRIME

A18. Please present an explanation/suggestion for why results appear to differ between PRIME2 and PRIME, e.g. WI-NRS improvement by ≥4 points from baseline to week 12 appears better in PRIME but WI-NRS improvement by ≥4 points from baseline to week 24 appears better in PRIME2, change in Skin Pain-NRS from baseline to week 24 and change in Sleep NRS from baseline to week 24 appear better in PRIME than PRIME2, etc.

Although the key endpoints between the trials differ slightly, they are consistent. It is unlikely that numerically identical outcomes will be achieved in studies that take place in different geographical settings even with replicate trials and taken at face value some endpoints in our data vary slightly. However, the data from PRIME and PRIME 2 are consistent between the two trials. In order to examine whether there is a statistically significant difference between studies we have carried out an analysis of study-by-treatment interaction p-values. The results of this are presented below.

These p-values assess if the dupilumab vs BSC treatment effect is statistically different between the PRIME and PRIME2 studies. The studies were not powered to detect an effect between them but in all cases any differences were not nominally significant suggesting that a pooled analysis of the data to provide more power in the determination of the individual endpoints is appropriate.

Analysis of the parameters mentioned in the question, WI-NRS improvement or reduction, Sleep NRS and Skin pain NRS, resulted in study-by-treatment interaction p-values of [redacted], [redacted], [redacted] and [redacted] respectively. None of these reached statistical significance.

Forest plots for the four analyses are provided below.

Figure 1. Responder analysis of WI-NRS improvement (reduction) >= 4 points from baseline at week 12 (primary method) – Pooled ITT population.

Notes: Odds Ratio (95% CI) and p-Value followed by a * is for Peto OR. Participants who received the prohibited medications/procedures and/or rescue medications that impacted efficacy before Week 12 were considered as non-responders, and missing data at Week 12 were considered as non-responders.

Figure 2. Responder analysis of WI-NRS improvement (reduction) >= 4 points from baseline at week 24 (primary method) – Pooled ITT population.

Notes: Odds Ratio (95% CI) and p-Value followed by a * is for Peto OR. Participants who received the prohibited medications/procedures and/or rescue medications that impacted efficacy before Week 24 were considered as non-responders, and missing data at Week 24 were considered as non-responders.

Figure 3. Figure of LS means change from baseline at week 24 (primary method) – Pooled ITT population – Sleep NRS.

Note: Data collected after study intervention discontinuation were included. Data post the select prohibited medications/procedures and/or rescue medications that impacted efficacy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF.

Figure 4. Figure of LS means change from baseline at week 24 (primary method) – Pooled ITT population – Skin pain NRS.

Note: Data collected after study intervention discontinuation were included. Data post the select prohibited medications/procedures and/or rescue medications that impacted efficacy were set to missing and imputed by WOCF. Missing data after study intervention discontinuation for lack of efficacy were imputed by WOCF.

Section B: Clarification on cost-effectiveness data

B1. Priority Question: CS, section B.3.2.2. Model structure.

The model is structured using the treatment response states 'Response' and 'No response'. Patients who receive BSC alone and are responders at the 24-week assessment time point enter the 'Response' treatment state.

1. **Please clarify why in patients who receive BSC alone, response to BSC is modelled separately from non-response over the long-term (after 24 weeks) when responders to BSC continue on BSC (i.e., the same treatment as non-responders).**

In the absence of published economic model data for PN a de novo model was developed for PN based on the model structures previously developed in the analogous disease area of AD. The AD model was originally developed to assess the cost-effectiveness of dupilumab in the treatment of AD. This was appraised by the NICE committee in August 2018 and a positive recommendation made (NICE TA534). After the 1st committee meeting the committee raised concerns that the model split 'responders' and 'non-responders' into different states for dupilumab, but not for best supportive care, and the model structure oversimplified the treatment pathway in people who had best supportive care (ACD section 3.25). An updated model was provided in response to this request. In line with the amended AD model, in the PN model patients on BSC arm are modelled separately in order to reflect the differences in utility achieved by those who respond to treatment and those who do not. In the clinical trials, there is a difference in quality of life between dupilumab responders and BSC responders Likewise, there is a difference in quality of life between dupilumab non-responders and BSC non-responders. After talking to clinicians and HEOR experts, we were advised that the best model structure is the one that is able to account for, and reflect, these differences. Therefore, we feel it is entirely reasonable to incorporate these differences in the economic model.

2. **Please explain why costs and utility values differ in BSC by response status when patients on BSC receive the same treatment regardless of response.**

In the absence of published economic model data for PN a de novo model was developed for PN based on the model structures previously developed in the analogous disease area of AD. The AD model was originally developed to assess the cost-effectiveness of dupilumab in the treatment of AD. This was appraised by the NICE committee in August 2018 and a positive recommendation made (NICE TA534). After the 1st committee meeting the committee raised concerns that the model split 'responders' and 'non-responders' into different states for dupilumab, but not for best supportive care, and the model structure oversimplified the treatment pathway in people who had best supportive care (ACD section 3.25). In the original model utility was pooled for responders and non-responders while resource use was handled separately. In response to the ACD Sanofi amended the model to handle non-responder and responder utilities separately, in line with the approach used with resource use. This new approach was accepted by the appraisal committee and this approach was supported by clinicians in advisory boards conducted in 2022.

We recognise that whilst the treatment regimen remains the same in the model regardless of responder status for BSC treated patients it is not unreasonable to expect that those patients who reach the efficacy response criteria and so may be considered less burdened by their disease, would have both different utilities and different resource use. This is reflected in the committee preferred approach from TA534 and is replicated in the current PN model.

B2. CS, section B.3.2.2. Model structure – timing of response assessment.

In the model, the exit time point from the decision tree is 24 weeks whereas the Markov model cycle length is 12 weeks, which suggests that the company expects response assessments to occur at 12-weekly intervals in clinical practice.

1. Please justify the use of a 12-week cycle length in the Markov model when an assessment time point of 24 weeks is used to assess treatment response.

The 12-week cycle length was chosen to make best use of the available data from PRIME and PRIME2. It is not predicated on the expectation that assessment in clinical practice would take place routinely every 12 weeks.

The primary endpoint in PRIME2 was proportion of patients with WI-NRS improvement (reduction) by ≥4 points from baseline to Week 12. The primary

endpoint in PRIME was proportion of patients with WI-NRS improvement (reduction) by ≥4 points from baseline to week 24. Moreover, the proportion of participants with an IGA PN-S 0 or 1 score at week 24 was a key secondary endpoint in both studies. In PRIME and PRIME2, assessments happened at 4, 8, 12, 24 and 36 weeks. The effect on itch due to dupilumab was expected to be significant by week 12 but the impact on nodules is very likely to take longer due to their fibrotic nature. Assessment at week 24 (i.e. 12 weeks later) in the model was intended to evaluate the continued benefit of treatment. This was judged by clinical expects to be long enough for the treatment effect to be established and maintained in responders with the expectation that those patients for whom dupilumab did not continue to provide the required level of benefit would discontinue. The clinical experts consulted during the advisory board conducted in December 2022 agreed the model structure is valid because the trial data demonstrated good response by 24 weeks and a notable significant difference between the dupilumab and BSC arms. They agreed that it was acceptable to begin the Markov model at week 24, since clinical response to WI-NRS and IGA were significant at week 12 but could be further enhanced by week 24. Participants in the trials didn't reach peak utility and peak response at week 12, therefore having the main assessment point at week 12 in the model would be too short a period by which to judge treatment benefit. Clinicians did not feel it appropriate to discontinue patients who had the potential to meet the response criterion too early.

Furthermore, in the clinical trials, the proportion of patients with significantly greater IGA scores in the dupilumab arm vs BSC arm was significant from week 8, however the greatest treatment difference was reported at week 24. This is in line with what we heard from clinical experts who explained that healing the nodules may take more time than the 12-week period.

2. Please provide the cost-effectiveness results for a scenario analysis where the assessment of response is conducted at 12 weeks after starting treatment rather than 24 weeks, in line with the company's expectation that response assessments will occur at 12-weekly intervals in clinical practice.

As explained in our response to B2.1 above we do not expect response efficacy assessment to be made for the purposes of treatment discontinuation at week 12

because this is too short a period to fully judge the benefit of treatment., Furthermore, assessment at 12 week is not supported by the trial data and clinical experts, however the requested scenario analysis is provided below. In this case the ICER decreases as the reduction in time on treatment results in lower costs.

The requested scenario analysis is provided below (Table 15).

Table 15. Cost-effectiveness results for scenario analysis with assessment of response at 12 weeks after treatment initiation

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Probabilistic							
BSC	[redacted]	[redacted]	[redacted]				
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,412
Deterministic							
BSC	[redacted]	[redacted]	[redacted]				
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,392

B3. Priority Question: CS, section B.3.3.2.1. Modelled efficacy response criteria.

1. **Please justify the use of the composite response criterion that combines WI-NRS improvement ≥ 4 with IGA-PN-S reduction ≥ 1 when the primary endpoint from the PRIME2 and PRIME trials was WI-NRS improvement ≥ 4.**

This This response criterion combines the primary endpoint from the PRIME2 and PRIME trials (WI-NRS score improvement ≥4) which measures the intensity of itch, with IGA (IGA PN-S score reduction ≥1) which assesses nodular lesion number and thickness. Use of this composite response criterion is a more holistic measure of the impact of disease than WI-NRS alone. The approach is preferentially supported over a single subjective measure such as WI-NRS by UK clinicians in the advisory board conducted by Sanofi in December 2022. It is also analogous to the composite response criterion (EASI50 and DLQI>4 points) for NICE appraisals in AD and other chronic immune mediated inflammatory diseases (including psoriasis and rheumatoid arthritis).

While WI-NRS and IGA PN-S, which are valid and reliable measures that have been validated for the use in PN, are not routinely used to assess response in current UK clinical practice, these tools are considered easy to implement by the clinicians who would like to use these criteria more frequently. This too is analogous to the increased use of the EASI score introduced on the implementation of the high-cost treatments in AD. It is worth noting that the composite endpoint of EASI 50 plus a >4 point improvement in the DLQI score for the assessment of response to AD treatment was considered to be the most appropriate holistic assessment of response during the original NICE assessment of dupilumab in AD. This was because it combined both signs and symptoms with the impact on HRQoL. Our approach for PN is aligned with this, it combines a PRO, assessing impact on itch (the most important determinant of HRQoL in PN) and an objective measure associated with the signs/ due to nodules. The importance of the combination of itch and impact of the nodules has been highlighted to us by clinical experts and people living with PN. Clinicians we have spoken to highlighted that they would support the use of a combination of objective and subjective measures as the main assessment point/response criteria in routine clinical practice). This is also in line with what has been approved used in psoriasis or rheumatoid arthritis models for other chronic immune mediated inflammatory diseases (such as AD, psoriasis and rheumatoid arthritis).

2. **Please clarify why the composite response criterion used in the model includes IGA-PN-S reduction ≥ 1 rather than IGA-PN-S score of 0 or 1 at week 24.**

Clinically, an IGA PN-S score of 0 or 1 corresponds to skin clear of nodules or almost clear, with only rare, flattened lesions.

Resolution of disease associated with achievement of IGA PN-S score of 0 or 1 requires remodelling and breakdown of significant lesional fibrosis. Fibrosis will only begin to heal once itching and scratching has ceased. Expert clinical advice suggested that it is very challenging in PN to reach IGA-PN-S score of 0 or 1 within 24 weeks, even with cessation of itch and scratching, due to the level of fibrosis in nodules. IGA-PN-S reduction ≥ 1 rather than IGA-PN-S score of 0 or 1 captures meaningful response at week 24.

In the pooled ITT analysis from PRIME and PRIME 2 the mean baseline IGA-PN-S score was [redacted] (IGA-PN-S ranges from 0 (clear) to 4 (severe)) denoting a significantly burdened population. For this population a reduction in IGA-PN-S reduction of ≥ 1 represents a significant impact on their disease activity. For example, moving from a IGA PN-S score of [redacted] to 2 or less constitutes a move to mild disease activity with mostly flattened lesions and fewer than 20 nodules. This would be regarded by many patients as a substantial and meaningful improvement.

3. **Please provide the week 24 response rates for dupilumab and BSC for the composite response criterion of WI-NRS improvement ≥ 4 and IGA-PN-S score of 0 or 1 using the 'as observed with multiple imputation (as observed + MI) method and pooled ITT analysis'.**

The 24-week response rates for dupilumab and BSC for the composite response criterion of WI-NRS improvement ≥ 4 and IGA-PN-S score of 0 or 1 using the 'as observed with multiple imputation (as observed + MI) method and pooled ITT analysis' is the following (Table 16):

Table 16. 24-week response rates for dupilumab and BSC for WI-NRS improvement ≥ 4 and IGA-PN-S score of 0 or 1 (as observed with multiple imputation method; pooled ITT analysis).

Technology	N responders at week 24, %
BSC	[redacted]
Dupilumab + BSC	[redacted]

4. **Please clarify how much data was missing from the PRIME2 and PRIME trials to inform the composite response criterion used in the model, why these data were missing, and how the missing data were classified.**

The requested analysis is now provided as Appendix to the submission. Please see Appendix 2 as attachment to our response document

5. **Please clarify what proportion of patients in the separate trial arms met the composite response criterion (i.e., responders to treatment) but still required rescue medication, and justify why these patients requiring**

rescue medication would continue to receive dupilumab treatment in clinical practice?

In the cost-effectiveness model we use the 'as-observed' approach in which patients do not withdraw from therapy, after use of prohibited medication/rescue therapy and the data is not censored. This is done to ensure that the modelled economic outcomes are as close to real world clinical practice as possible. This methodological choice explains why some patients who are responders may receive dupilumab treatment for some time, as they would in UK clinical practice.

Extensive analysis is provided as an Appendix. Please see Appendix 2 as attachment to our response document.

6. **Please clarify why an improvement in the DLQI score is not considered part of the response criterion.**

The dermatology-specific DLQI is a quality of life measure which may quantify humanistic burden in patients with PN. As seen in the clinical trials, treatment with dupilumab significantly increased patient HRQoL, reported as a DLQI decrease from baseline to Week 12 and Week 24, in both the individual PRIME2 and PRIME studies and in the pooled ITT analysis compared to BSC. However, clinical experts at the April 2022 advisory board highlighted that the introduction of dupilumab might prompt the need for a subjective measure that is more specific to PN which captures the key impact of itch, rather than using the more general DLQI. The experts highlighted that WI-NRS is a subjective measure appropriate to this key impact on patients' quality of life.

As with the efficacy response criteria now commonly accepted for AD (See below) the experts also agreed that this subjective measure should be combined with an objective measure such as IGA PN-S. This combination is the optimal way towards a holistic approach for efficacy assessment as it provides a snapshot of the impact on the key determinant of QoL from the patient perspective and a measure of 'signs and symptoms' formed by clinician opinion. Two subjective measures such as DLQI and WI-NRS would not provide the breadth of coverage need to make a judgement on whether treatment was effective.

This adoption of a holistic assessment has already been implemented in atopic dermatitis. In this case, the EASI score and the DLQI as a combined efficacy response criterion only became routinely used following the introduction of dupilumab and is now firmly established for all high-cost drug AD assessments. At the time clinical experts considered DLQI was an appropriate subjective measure for AD. However PN is different, but experts expect the related combined efficacy response measure which incorporates WI-NRS and IGA-PN-S in PN. Furthermore, they suggested that using more than two measurement scores would be unfeasible and impractical in routine clinical practice.

In the light of this advice received from clinical experts we have chosen the combination of WI-NRS and IGA-PN-S as the most appropriate efficacy response criterion.

Please also see response above about use of subjective measures in clinical practice in the UK (B3, question 1).

B4. Priority Question: CS, section B.3.3.2.3. Annual discontinuation rates. The model uses the pooled all-cause discontinuation rate from PRIME2 and PRIME as a proxy for long-term loss of treatment response.

1. **Please justify why the response rates observed over the 24-week period of the clinical trials is a good proxy for long-term discontinuation rates, particularly in light of: (i) the improved adherence to treatment and access to healthcare facilities and professionals in the protocol-driven clinical trial setting; and (ii) the fact that the discontinuation rate for loss of response in the trials is already reflected in the percentage of responders at week 24.**

We received advice from health economic and clinical experts to use all-cause discontinuation for discontinuation rates in the model, as observed in the trials, given this is the best available data and a good proxy. In an April 2022 advisory board, potential effect of the increased adherence was discussed with the experts. The clinical experts highlighted that discontinuation in the trials is low. This can partly be explained by the selection process in clinical trials. Also, patients are generally motivated to continue on in clinical trials because they are expecting a response.

However, the health economic expert highlighted that it is common for discontinuation rates in clinical trials to be low. Therefore, the panel's suggested to use all-cause discontinuation from the trials for the probability of movement between responder and non-responder states.

Given the relatively short trial follow-up and limited data availability the other option would be mathematical extrapolation, which would use assumptions instead of observed clinical trial data. In order to account for this uncertainty, different scenarios have been tested for discontinuation. We have presented a scenario analysis in the main submission using long-term, observed discontinuation rate from the AD CHRONOS placebo controlled clinical trials. Furthermore, all-cause treatment discontinuation is used as a proxy for loss of response in the model. Thus, the trial-observed discontinuation rates are used as transition probabilities from "response" to "no-response" in the Markov portion of the model.

2. **Please clarify whether the pooled all-cause discontinuation rate from the trials includes participants who discontinued treatment because they required rescue medication.**

In the PRIME2/PRIME clinical trials participants who discontinued treatment because they required rescue medication, were deemed non-responders.

All cause discontinuation used in the model includes discontinuation events due to patient/physician preference, adverse event, loss of response. Data used in the model is not censored data.

3. **Please clarify why the model includes <u>both</u> an annual discontinuation rate for long-term loss of treatment response and a probability of sustained response per year (i.e., assumptions regarding response waning over time where treatment responders in the model move from the 'Response' to 'No response' state).**

The annual discontinuation rate in the model is implemented as a transition probability from "response" to "no-response" in the Markov portion of the model. However, the concept of loss of treatment response for patients with PN after exiting the controlled clinical trial environment has also been explored and modelled. We

have used the methodology agreed in the series of AD appraisals carried out by NICE, including the single technology appraisals for dupilumab (TA534) and baricitinib (TA681), and in the multiple technology appraisal for upadacitinib, abrocitinib and tralokinumab.

In the pooled analysis of the PRIME2 and PRIME trials, there was a high treatment response rate in both the BSC and dupilumab arms (see main submission Document Section B.2), similar to what was seen in the AD clinical trials. This is also generally well recognised in the dermatology clinical trial literature. We argue that it is improbable that the observed effect size for BSC alone would persist once patients have completed the trials and are outside the protocol-driven clinical trial setting where behaviours, particularly around the adherence to topical treatments, are mandated. Also, in routine clinical practice after leaving the trial protocol, patients are likely to either stop or switch to other treatments if their current treatment is no longer effective or has side effects. The concept of loss of treatment response was incorporated in the model to account for removal of the protocol driven trial effect at this point and was supported by clinical expert opinion.

Please also note the model is not sensitive for the discontinuation rate applied, to account for uncertainty, a scenario using AD discontinuation rate is provided in the main submission.

B5. Priority Question: CS, section B.3.3.2.2. Long-term treatment effect and response waning.

1. **Please provide justification for using long-term response waning rates for dupilumab in AD as a proxy for sustained response in PN.**

The model is designed to estimate the long-term benefit of treatment beyond the extent of the observed trial evidence. As there are no extension studies to allow for estimation of the real-world effectiveness of dupilumab or BSC in PN, the probability of sustained response (and maintenance of HRQoL) must be extrapolated. The PRIME2 and PRIME trials are the largest PN clinical trials conducted to date and demonstrate the efficacy and tolerability of dupilumab versus BSC in improving symptoms of PN. However, long-term data is not available for PN.

The model is designed to estimate the long-term benefit of treatment beyond the extent of the observed trial evidence. As there are no extension studies to allow for estimation of the real-world effectiveness of dupilumab or BSC in PN, the probability of sustained response (and maintenance of HRQoL) must be extrapolated. The PRIME2 and PRIME trials are the largest PN clinical trials conducted to date and demonstrate the efficacy and tolerability of dupilumab versus BSC in improving symptoms of PN. However, long-term data is not available for PN.

PN and AD are similar chronic, type 2 inflammatory skin diseases requiring long-term management in which assessment for treatment response to biologic therapy is expected after six months following treatment initiation. The two diseases have a comparable impact on patient HRQoL. This is supported by clinical expert opinion.

In the absence of other evidence for sustained treatment effect in the PN therapy area we consulted with clinical experts to understand if patients with PN would maintain the HRQoL benefit over a longer period after returning to real-world clinical practice. Clinicians in the UK, who have experience of the use of dupilumab for the treatment of AD, expect benefits associated with dupilumab response in PN to be maintained in a post-trial setting for patients who continue to receive treatment. Given that long-term evidence for dupilumab is available from the AD OLE study (Appendix T) and this study demonstrates maintained treatment effect and sustained (or even improving) HRQoL (as expected by clinical experts) in PN it is appropriate to use these data in the absence of other evidence. Furthermore, the OLE for AD is the most robust data available for long-term treatment with dupilumab in a similar disease area and was confirmed as the preferred data for response waning with dupilumab in the global advisory board conducted in April 2022.

2. **Please clarify why the probability of sustained response for dupilumab is greater in year 3 compared to the other years (Table 23), and why there is expected to be no loss of response in the first year?**

The AD long-term study is the best available long-term study to date, collecting data up to 4 years. The values used in the model come from the associated long-term safety and efficacy OLE study was published in 2022 (Beck, 2022). For the purposes of the modelling changes within year 1 are not explored because we expect the

week 24 responders to keep their response until the end of year 1. After this the response waning rates are applied at year 2+. The values in Table 23 in the submission dossier are the conditional probability of sustained response based on responder status in the previous year. In year 3 according to the data collected in the OLE study, there was a lower rate of loss of efficacy than in other years explaining why this value is higher.

In order to account for the uncertainty in the data, we tested a flat rate using value of Year 4 (90.9%) for Year 3, 4 and 5 (90.9%) in a scenario analysis, please see associated analysis below: This had minimal impact on the ICER, please see associated analysis below (Table 17).

Table 17. Cost-effectiveness results for scenario analysis with a response rate 90.9% for Years 3 to 4.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Probabilistic							
BSC	[redacted]	[redacted]	[redacted]				
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,920
Deterministic							
BSC	[redacted]	[redacted]	[redacted]				
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,908

3. **Please explain why <u>both</u> a response waning effect is included for BSC in the model (Table 24) and a waning effect on utility values for non-responders (i.e., the proportion of utility maintained at time intervals of 0-6 months, 6-12 months, 1-2 years, and 2+ years based on values from the structured expert elicitation exercise).**

The concept of response waning is implemented and used so the proportion of responders/non-responders can be accurately determined in the economic model. This concept was accepted by NICE in a similar disease area, AD and it is widely supported by UK based clinical experts for PN.

The concept of utility waning is introduced into the model to account for the loss of associated benefits, realised in people's quality of life. The utility waning has been implemented based on clinical expert opinion received during our structured expert

elicitation. Applying utility waning in the model is a conservative approach. In line with expert opinion utility is diminishing quickly after discontinuation on active treatment, negatively affecting the ICER.

In order to account for the uncertainty around the waning used in the model, we have presented scenario analysis in the submission, please see section B.3.8.3 Scenario analysis, Table 52.

B6. Priority Question: CS, section B.3.4.2.1. Health-related quality of life (HRQoL) utility values used in the model.

1. **Please provide further details on the methodology used to derive the utility values presented in Table 29. Specifically:**

    a. **Please clarify how the predictor variables of DLQI and WI-NRS score were chosen, and whether any other variables such as IGA-PN-S score may be candidates due to correlation with HRQoL.**

Please see response in 'Health utility (Quality-of-life) estimation in PN clinical trials' summary document in Appendix 8.

    b. **Please clarify how the baseline variables were chosen, and whether consideration should be given to controlling other baseline variables such as baseline WI-NRS and IGA-PN-S scores.**

Please see response in 'Health utility (Quality-of-life) estimation in PN clinical trials' summary document in Appendix 8.

    c. **For the estimation of EQ-5D utility values, please provide details on the level of data available at each time point (baseline, week 12 and week 24) for both arms of the pooled clinical trials (e.g., the number of patients with each outcome at each time point used for the derivation of EQ-5D utility values).**

Table 18. EQ-5D single index score in the pooled ITT population.

	EQ-5D-5L from PRIME2 and PRIME trials	
	BSC	**Dupilumab**
Baseline	**N=156**	**N=153**
Mean (SD)	0.640 (0.258)	0.621 (0.261)
Median	0.725	0.725
Week 12	**N=153**	**N=152**
Mean (SD)	0.72 (0.20)	0.76 (0.22)
Median	0.77	0.79
Week 24	**N=145**	**N=152**
Mean (SD)	0.72 (0.22)	0.76 (0.22)
Median	0.77	0.80

BSC = best supportive care; EQ-5D-3L = Euroqol 5-dimension 3-level; EQ-5D-5L = Euroqol 5-dimension 5-level; ITT = intent-to-treat; SD = standard deviation; UK = United Kingdom

d. Please provide full details on the methodology used for missing EQ-5D-5L participant data at follow-up time points.

Data collected after study intervention discontinuation and/or after taking the select prohibited medication/procedures and/or rescue medications were included, and missing data were imputed by MI.

2. Please explain why there is a significant improvement in HRQoL from baseline on BSC at both 12 and 24 weeks, even for non-responders to BSC.

a. Please clarify whether the improvements in HRQoL for BSC in Table 29 are expected to be a result of better adherence to BSC in the protocol-driven clinical trial setting.

In previous NICE appraisals in an analogous disease area, AD, long-term HRQoL has been recognised as a key area of uncertainty. For the appraisal of dupilumab in AD, a brief survey of clinical experts was conducted to elicit the expected baseline utility values for both arms, and the rate at which patients would return to that baseline. The centre of the argument is that it is improbable that this effect size for BSC alone would persist once patients have completed the studies and are outside

the protocol driven clinical trial setting where behaviours, particularly around the adherence to treatments, are mandated.

As expected, this uplift is also observed in the PRIME clinical trial programme too. Increases in HRQoL in the placebo arm throughout the trial are evident and highly likely to be caused by several factors, including: improved adherence to treatment due to regular clinic visits and increased access to healthcare facilities and professionals both as mandated in the trial protocols. Access to optimal best supportive care whilst on treatment and timely rescue therapy are also key factors. Hence the HRQoL observed in study patients is higher than might be expected and unlikely to be achievable with current therapeutic options in real world clinical practice. Clinicians we have spoken to have expressed an even stronger belief that this effect will be observed in the PN therapy area versus AD.

b. Please explain why there is a large difference in the mean change from baseline DLQI and WI-NRS scores between responders and non-responders to BSC.

PN is a disease area with few treatment options. Experts suggested that this is likely to happen because non-responders' skin disease is active even during the trial period. Experts also noted that HRQL improvement in this subgroup of patients during the trial is expected to be the lowest.

c. Please clarify why a pooled (across response status) utility value for BSC, weighted by the proportion of responders at week 24, was not implemented in the model.

After the 1st AD committee meeting the committee raised concerns that the model split 'responders' and 'non-responders' into different states for dupilumab, but not for best supportive care, and the model structure oversimplified the treatment pathway in people who had best supportive care. In the original model utility was pooled for responders and non-responders while resource use was handled separately. In response to the ACD Sanofi amended the model to handle non-responder and responder utilities separately, in line with the approach used with resource use. This new approach was accepted by the appraisal committee. We are using the same approach accepted by the committee in the PN model.

The Markov model is designed to mirror the long-term treatment effect, clinical expert opinion is that BSC responders could still experience a HRQL benefit after exiting the trial, and may have developed a more effective topical regimen during the trial that they will maintain after the trial, therefore maintaining some HRQL. Additionally, while HRQL is likely to erode over time post-trial, the experts expected a slow loss of effect as the treatment itself is effectively unchanged, compared those who are non-responders.

3. **Please justify the use of a constant utility value over time (from week 24) for responders to dupilumab treatment that is equivalent to the pooled estimate from the PRIME2 and PRIME trials at week 24 for dupilumab responders in light of the improved adherence to treatment and access to healthcare facilities and professionals in the protocol-driven clinical trial setting.**

The value of dupilumab in PN is expected to manifest as improvements in the signs and symptoms of the disease, resulting in long-term gains in health-related quality of life (HRQL). This is primarily evidenced by differences observed in HRQoL, as measured using EQ-5D, in the pivotal Phase III clinical trials (PRIME2 and PRIME1), which compared dupilumab with placebo in patients with PN over 24 weeks. Clinicians in the UK expect HRQoL improvements associated with dupilumab response to be maintained post-trial in patients who continue to receive treatment. The clinicians we have spoken to concluded that dupilumab response would be maintained post trial and that based on the OLE study data for AD (indeed, HRQoL was observed to rise in the longer-term during the OLE) and clinical experience, there is no reason to believe that the HRQoL of patients who continue to respond and remain on dupilumab would decrease over time.

4. **For the utility value of dupilumab responders at week 24, please clarify why the utility improvement associated with BSC is not subtracted from the utility improvement associated with dupilumab responders, in recognition of the fact that part of the response for dupilumab treatment which includes BSC is due to the BSC response.**

The analysis provided in our submission is an incremental analysis. Benefit associated with BSC use is incorporated in both arms and so differentially removing the BSC benefit from the dupilumab arm would result in an unbalanced analysis. This is the case for utility values, and for costs.

5. **Please clarify why the utility values for dupilumab non-responders when they move to BSC remains higher than the utility values for BSC, even after 5+ years loss of treatment response.**

The utility values in the model are adjusted based on the responses provided by the experts during the SEE exercise. Experts anticipated some residual utility improvement in the long-term with dupilumab for those who stopped taking the drug, this expert opinion is implemented in our model.

6. **Please clarify what aspects of social functioning for moderate-to-severe PN are not captured in the dimensions of the EQ-5D-5L.**

EQ-5D-5L provides a snapshot of a person's functioning relating to the individual's circumstances on the day the instrument is administered. An aspect of, "social functioning" in practice includes the ability of a person to plan for the future in relation to their own socioeconomic situation. In this regard, EQ-5D-5L does not precisely capture forward-looking social aspirations or socioeconomic ambitions, i.e., the instrument does not provide information about how a condition affects someone's forward-looking social aspirations as well as the extent of the poverty of aspiration created by living with moderate-severe PN. For example, someone living with moderate-severe PN may feel that the condition has limited their future ambitions and aspirations. They may feel less empowered as a consequence of their moderate-severe PN which is visible to other people, to pursue education, work experience or employment which could lead to improved 'life chances'.

B7. CS, sections B.3.3.2.2.4 Structured expert elicitation (SEE). STEER guidance indicates that a minimum of five experts should be identified. Company submission states that "six experts were invited, of whom four took part in the exercise.

However, the analysis was based on answers from three experts only. One clinician was lost in follow-up" (p.75).

1. Please provide details on how these three experts reflect the full diversity of opinion across relevant dermatology experts treating PN in UK clinical practice, and justify the deviation from STEER guidance on the number of experts included.

Eliciting HRQL benefit maintained after trial completion/discontinuation from clinical experts presents a challenge, as clinicians do not normally measure HRQL in standard clinical practice. Best efforts were made to quantify HRQL using the STEER guidance. To ensure that the quantities of interest were 'observable' to the experts, such that they could provide meaningful judgements, we targeted experts with substantial experience of treating patients with PN in UK clinical practice, ideally with experience within the PRIME/PRIME2 studies. There was, however, only one active clinical trial site in the UK where screening was performed, which would have limited the total expert pool to two experts. Both of these experts were contacted, one of whom participated in the study, while the second was unavailable.

To increase the sample size, we therefore expanded our eligibility criteria to include other experts that did not partake in the PRIME/PRIME2 trials. Of the three additional experts, one had experience within a previous PN trial for nemolizumab, and one was part of the committee that developed the PN guideline for the British Association of Dermatology, and the third is a consultant dermatologist with over 10 years of experience treating patients with PN.

Although the sample size for this study is lower than the 5 recommended within STEER guidance/the MRC protocol, it is reasonable to believe that the diversity of opinion is reflected within this study given that (i) the total expert pool is limited due to the rarity of PN, and (ii) one of the two experts with UK PRIME/PRIME2 experience was recruited. This is supported by the considerable between-expert variability observed for some of the quantities of interest. For example, for HRQL benefit maintained in dupilumab non-responders 6m after trail completion, the plausible ranges provided by the experts were [redacted], [redacted], and [redacted], representing substantial differences in opinion

2. Please justify the use of the three distinct time points (six months, one year and ≥two years) after trial used in the SEE.

The time points were selected based on a consultation with a clinical expert familiar with both PN and the use od dupilumab in AD. Though HRQL waning was assumed to occur over a 5-year period in the NICE appraisal of dupilumab for atopic dermatitis (TA534), the expert noted that this would take place over a shorter period in PN, primarily due to the greater challenges with adherence in this patient group. The expert advised that the majority of the HRQL benefit would be lost within 2 years of trial completion/discontinuation, which was indeed reflected in the results. A 1-year timepoint was selected given that the model cycle length was one year at the early planning stages. Finally, the 6-month timepoint was included to gain an understanding of short-term HRQL dynamics, given that HRQL was expected to change most within the first year.

3. Please provide details about the challenges associated with eliciting the unobservable quantity of the proportion of HRQoL maintained after treatment discontinuation, and the challenges for clinical experts to express their uncertainty over these values.

The York protocol states that quantities of interest should be expressed as ‘reasonably observable’. However, as noted above, patient utility may be difficult to observe on a routine basis for clinical experts given that it is not measured in standard clinical practice, creating challenges in obtaining definitive results. To ensure that the quantities of interest were as observable as possible, we (i) prioritized recruitment of experts who participated in the PRIME/PRIME2 clinical trials, and (ii) framed the quantities of interest as the percentage of overall HRQL maintained relative to baseline (0%) and completion (100%) of PRIME/PRIME2. This removes the need for experts to provide estimates in absolute utility values. Furthermore, the patient population was divided by treatment arm and response status. Experts were familiar with the criteria for response and would have had first-hand experience of patients transitioning from meeting the criteria for response to non-response. Therefore, we believe the quantities of interest are ‘reasonably observable’ to this group of experts. However, we acknowledge that it remains

uncertain whether clinicians can accurately assess the HRQL of patients, even relative to pre-defined situations, and this remains a limitation of the study.

4. Please clarify why there are greater challenges with adherence to dupilumab treatment in PN compared to AD (page 75 of CS) that would give rise to treatment waning occurring over a shorter period in PN.

Clinical experts highlighted to us that people with PN experience intense itch. Itch is considered the most defining and impactful symptom of PN by clinicians in the UK. There is also a substantial negative impact on people's lives due to the physical appearance, owing to presence of persistent nodules. Experts highlighted to us that people usually jump from department to department and constantly giving up when the available treatments have little effect on reducing the appearance of nodules. The expert who participated in a recent qualitative interview noted that adhering to multiple corticosteroids on a daily basis is burdensome for people and they are in the expert's opinion less adherent to their treatment regimens, compared to AD. Hence, a quicker decrease in HRQoL is expected on return to the real-world clinical practice setting.

B8. CS, section B.3.5.6.1.2. Rescue medication costs.

1. Please justify why the frequency of rescue medications used by patients in the PRIME2 and PRIME trials is reflective of that likely to be seen in clinical practice outside of the protocol-driven clinical trial setting.

The number of patients using rescue medications was available from the clinical trials (PRIME, PRIME2). We combined this information with (i) the relevant acquisition costs, (ii) posology data and (iii) assumptions regarding the average duration of rescue treatment. Rescue medication use from the clinical trial is the best available proxy for use of rescue treatments in real word. Clinical experts who participated in the April advisory board highlighted that in usual clinical practice they would use rescue drugs (drugs that deemed to be rescue drugs in the clinical trial environment) more frequently for non-responders, therefore the cost for non-responders in the model is underestimated.

2. Please clarify whether the frequency of rescue medications used by patients in the PRIME2 and PRIME trials is based on a 12-week or 24-week period. If

12-weeks, please explain why the pooled frequency of rescue medications was not based on the 24-week period that marked the intervention period of the trials. If 24-weeks, please explain why the total cost of rescue medication calculated in the model per 12-weeks is based on frequency of use over a longer time period.

The frequency of rescue medication used by patients in the PRIME2 and PRME trials is based on a 24-week period, this was incorrectly applied in the model, which we have now corrected. Please see base-case analysis provided below with the correction. This had minimal impact on the ICER.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Probabilistic							
BSC	[redacted]	[redacted]	[redacted]				
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,974
Deterministic							
BSC	[redacted]	[redacted]	[redacted]				
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,009

3. Please provide justification for the duration of rescue medication every 12 weeks in the model.

The duration of rescue medication in the model was based on an assumption. Treatment duration generally, conservatively, assumed to be 2-weeks, except (i) where BNF dose is incompatible with a 14-day course, or (ii) where the drug would be expected to need more than 14 days to take effect (e.g. anti-depressants).

Section C: Textual clarification and additional points

C1. There appears to be an error on page 43 – B.2.6.2: week 12 result [redacted], week 24 result 53.44% vs 27.97% - should [redacted], (assuming the change the results refer to is the LS mean percentage reduction in WI-NRS)?

Please see corrected text below:

In the pooled ITT analysis, the LS mean percentage change in WI-NRS was significantly greater in the dupilumab group compared to the BSC group both from baseline to Week 12 [redacted] and from baseline to Week 24 (53.44% vs. 27.97%; nominal p<0.0001).

Search strategies

C2. For the clinical evidence searches and health-related quality of life searches (Appendix D), please provide the search strategies for the searches of conference proceedings, or clinicaltrials.gov.

Conference abstracts were searched as part of the database searches as they were indexed in Embase via Ovid. The search of clinicaltrials.gov is shown in Table 19 below.

Table 19. Database search of clinicaltrials.gov.

Search source	Search terms	Hits
Clinicaltrials.gov	Prurigo Nodularis	30

C3. For the cost-effectiveness searches and cost and healthcare resource searches (Appendix G), please provide the search strategies for the searches of professional organisations, healthcare organisation websites, NHS EED (or any other CRD databases searched, if applicable), or the School of Health and Related Research Health Utilities Database.

All professional organisations and health organisation websites listed as sources were searched using prurigo nodularis as the search term.

Search strategies used for the NHS EED and ScHarrHUD are the following (Table 20 and Table 21):

Table 20. Centre for Reviews and Dissemination, NHS EED (Search conducted on 28th July 2021).

Search number	Search terms	Hits
Population		
#1	MeSH DESCRIPTOR Prurigo EXPLODE ALL TREES OR ("prurigo nodularis" OR "nodular prurigo" OR ((prurigo OR pruritus) AND nodular*))	**0**

Table 21. ScHarrHud (search conducted on 28th July 2021).

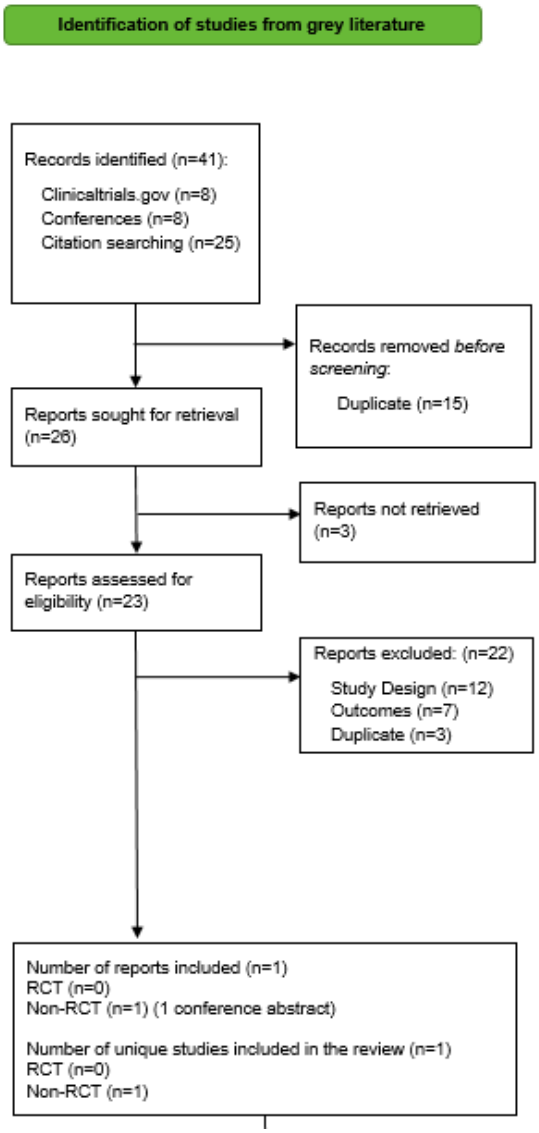
Search number	Search terms	Hits
Population		
#1	(("prurigo nodularis" OR "nodular prurigo" OR ((prurigo OR pruritus) AND nodular*)))	**0**

C4. Please provide the strategies for the targeted literature review (TLR) of cost-effectiveness studies which is referred to on p 61 of 'ID4054_Dupilumab_Document B_09022023_ACIC'. The aim of the TLR was to identify models in pruritus, targeted literature review was done in PubMed on 2nd July 2021 using the following search criteria: <<((cost) OR (economic)) AND ((pruritus) OR (itch))>>

C5. The PRISMA diagram (Figure 1) on p. 14 of Appendix D, details both RCT searches and non-RCT searches to find clinical evidence and health-related quality of life evidence respectively. However, only the database searches appear in the PRISMA diagram, even though evidence was sought from a range of other sources. Notably p. 13 of Appendix D describes findings of 2 RCTs on clinicaltrials.gov but these do not appear in the PRISMA diagram. It is also not clear which exact sources were searched for these different study types (RCT vs non-RCT).

PRIME and PRIME2 studies were not included in the review as grey literature, as results were not published on clinicaltrails.gov at the time of search. Grey literature search returned one conference abstract that was included within the data extraction phase: Hitosugi (2021) The Effect of Combined Therapy of Topical Anesthesia and Capsaicin Ointment in Prurigo Nodularis Management.

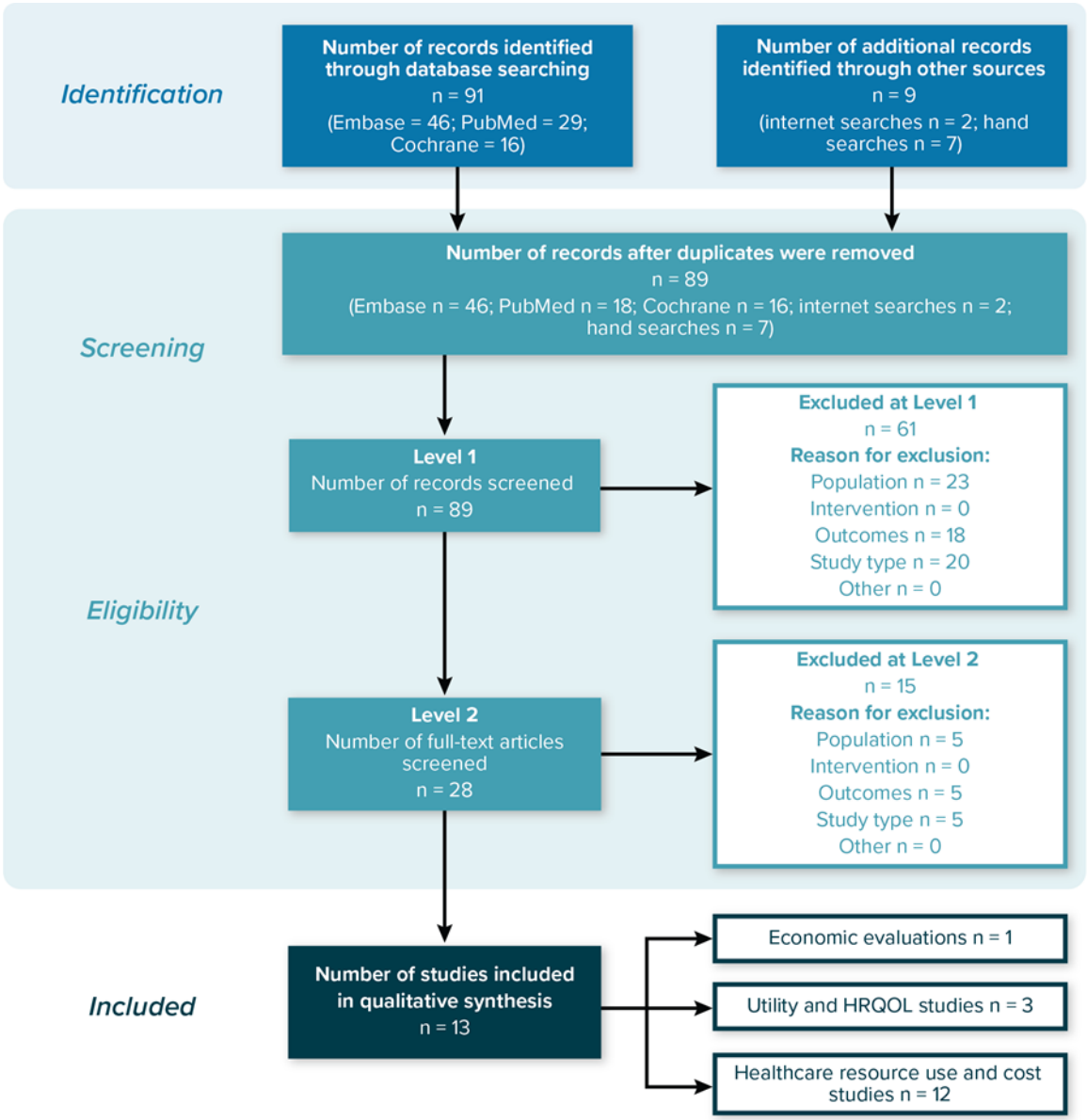
The PRISMA diagram is included below for the grey literature search for reference.



C6. For the cost-effectiveness searches and cost and healthcare resource searches (Appendix G), only the searches of Embase, PubMed and Cochrane appear in the PRISMA diagram, even though evidence was sought from a range of other sources. These are all lumped together as 'other sources', please state each source, followed by the number of records found (including if none were found).

Please see below for the PRISMA with the other sources split out, however, there were no records to include from other sources in the review (Table 22 and Table 23).

Figure 5. PRISMA results for searches of the Embase, PubMed and Cochrane databases.



The sources of the “other sources” searched were as follows:

Table 22. Sources searched in the hand searches.

Full reference	Number of potentially relevant studies	Number screened after exclusion of duplicates
Hendricks AJ, Yosipovitch G, Shi VY. Dupilumab use in dermatologic conditions beyond atopic dermatitis–a systematic review. J Dermatolog Treat. 2021;32(1):19-28. Doi:http://dx.doi.org/10.1080/09546634.2019.1689227.	5	5
Janmohamed SR, Gwillim EC, Yousaf M, Patel KR, Silverberg JI. The impact of prurigo nodularis on quality of life: a systematic review and meta-analysis. Arch Dermatol Res. 2020. Doi:http://dx.doi.org/10.1007/s00403-020-02148-0.	2	2
Table Ekelem C, Juhasz M, Khera P, Mesinkovska NA. Utility of naltrexone treatment for chronic inflammatory dermatologic conditions: a systematic review. JAMA Dermatol. 2019 Feb 1;155(2):229-36. Doi:http://dx.doi.org/10.1001/jamadermatol.2018.4093.	0	0
Total	**7**	**7**

Table 23. Results of the internet searches.

Conference	Details	Date of search	Search terms used	Total publications identified in initial search (N)	Total publications potentially relevant (N)
Conference websites					
ISPOR	ISPOR 2021	NA	Indexed in Embase (found in Value in Health)	NA	NA
	ISPOR 2020		Indexed in Embase		
	ISPOR 2019		Indexed in Embase		
European Academy of Dermatology and Venereology Congress	2021	NA	To be held in September 2021	NA	NA
	2020		Indexed in Embase		
	2019		Indexed in Embase		
American Academy of Dermatology	2021	NA	To be held in August 2021	NA	NA
	2020		Indexed in Embase		
	2019		Indexed in Embase		

British Association of Dermatologists	2021	28 Jul 2021	Prurigo Nodularis	0	0
	2020	NA	Indexed in Embase	NA	NA
	2019	NA	Indexed in Embase	NA	NA
International Conference on Dermatology and Dermatologic Diseases	2021	NA	To be held in September 2021	NA	NA
	2020	28 Jul 2021	Prurigo Nodularis	0	0
	2019	28 Jul 2021	Prurigo Nodularis	0	0
Australasian College of Dermatologists	2021	NA	Indexed in Embase (Held in April 2021)	NA	NA
	2020		Indexed in Embase		
	2019		Indexed in Embase		
Health technology assessment websites					
NICE		28 Jul 2021	Prurigo Nodularis; Limits: none	28	2
SMC		28 Jul 2021	Prurigo Nodularis; Limits: none	0	0
CADTH		28 Jul 2021	Prurigo Nodularis; Limits: none	1	0
HAS		28 Jul 2021	Prurigo Nodularis; Limits: none	0	0
INAHTA		28 Jul 2021	Prurigo Nodularis; Limits: none	0	0
Tufts Medical Center CEA Registry		28 Jul 2021	Prurigo Nodularis; Limits: none	0	0
EUnetHTA		28 Jul 2021	Prurigo Nodularis; Limits: none	0	0
Total				**29**	**2**

CEA = cost-effectiveness analysis; HAS = Haute Autorité de Santé; INAHTA = International Health Technology Assessment Database; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NA = not applicable; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium.

C7. For the clinical evidence searches and health-related quality of life searches (Appendix D), please provide data on the database segment, or years of coverage, for Medline via Ovid or Embase via Ovid.

The searches were conducted on December 16th, 2022 with no lower limit to publication date. The search date is shown in Table 24 and Table 25.

C8. For the cost-effectiveness searches and cost and healthcare resource searches (Appendix G), there is no description of the platform EconLit or the Cochrane Library databases were searched on – please provide details.

There were no hits identified in the EconLit database and 16 hits identified from the Cochrane Library, see Table 24 and Table 25 below.

Table 24. EconLit library literature search strategy (conducted on 16 December 2022).

Search number	Search terms	Hits
Population		
1	SU Prurigo OR TX ("prurigo nodularis" OR "nodular prurigo" OR ((prurigo OR pruritus) AND nodular*))	**0**

Table 25. Cochrane library literature search strategy (conducted on 16 December 2022 via Ovid).

Search number	Search terms	Results
1	(prurigo nodularis or nodular prurigo or ((prurigo or pruritus) adj4 nodular$)).ti,ab,kw.	75
2	(cost analysis or cost-analysis or (cost effective* or cost-effective*) or (cost utility or cost-utility) or (econometric or (value adj2 (money or monetary)))).ti,ab,kw.	32015
3	(modeling or modelling or economic model* or (costminimization or costminimisation or cost-minimisation or cost-minimization or cost minimization or cost minimisation or (model* and (cost* or econom* or pharmacoeconomic*))) or (budget impact or markov) or decision analysis or discrete event simulation or (Monte Carlo method or Monte Carlo model or Monte Carlo simulation or Monte Carlo technique)).ti,ab,kw.	27925
4	(economic evaluation or (cost$ and (effective$ or utilit$ or benefit$ or minimi$))).ti,ab,kw.	55180
5	1 and (2 or 3 or 4)	0
6	(healthcare cost$ or health care cost$ or health-care cost$).ti,ab,kw. or economic$.ti. or (pharmacoeconomic$ or pharmaco-economic or pharmaceutical economics or "resource use" or resource utilization or resource utilisation or cost).ti,ab,kw. or budget$.ti,ab,kw.	69188
7	(expenditure$ or resource utili$ or ("health care use" or "healthcare use" or "health service use" or "health services use" or health care utilisation or healthcare utilisation or healthcare utilization	43114

	or health resource utilization or health resource utilisation or health service utilisation or health service utilization or health services utilisation or health services utilization or ((direct or indirect) and cost$) or medication cost$ or physician cost$) or (hospitalisation cost$ or hospitalization cost$ or hospital cost$ or length of stay$ or patient admission or hospital admission)).ti,ab,kw.	
8	(productivity cost$ or productivity los$ or (societal cost$ or economic benefit$) or employment or (unemployment or (loss adj2 work)) or absenteeism or (presenteeism or (productivity and (cost$ or costs)))).ti,ab,kw.	10430
9	1 and (6 or 7 or 8)	0
10	(health utility or health utilities or standard gamble or (time trade off or time trade-off or tto or disutilit$ or (utilit$ adj3 (valu$ or measur$ or health or life or estimat$ or elicit$ or disease or score$ or weight)))).ti,ab,kw.	3393
11	(euroqol or (euroqol 5d or eq5d$ or eq 5d$ or eq-5d$) or (assessment of quality of life or aqol or quality of well being or quality of well-being or qwb or qwb-sa or quality of well being self-administered or quality of well-being self-administered or quality of well-being-self-administered or quality of well being-self administered or 15d or 15-dimensional or 15 dimensional or fifteen-dimensional or fifteen dimensional) or (health utility index or health utilities index or (health and utilit$ and index))).ti,ab,kw.	14105
12	(sf-6d or sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw.	16211
13	(qaly or (quality adjusted life year or quality adjusted life years or quality adjusted life-year or quality-adjusted life-year or quality-adjusted life years or quality adjusted life-years or quality-adjusted life-years or daly or dalys) or (disability adjusted life year or disability adjusted life years) or (willingness to pay or (utilit$ and score$) or (utilit$ and weight$) or (health$ adj2 year$ adj2 equivalent$))).ti,ab,kw.	11549
14	(Nottingham Health profile or (sickness impact profile or health utilities index or HUI$ or caregiver burden)).ti,ab,kw.	2891
15	1 and (10 or 11 or 12 or 13 or 14)	16
16	5 or 9 or 15	16

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Dupilumab for treating prurigo nodularis [ID4054]
Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted] on behalf of the British Association of Dermatologists' Therapy & Guidelines sub-committee and BAD guideline development group for nodular prurigo
2. Name of organisation	British Association of Dermatologists (BAD)
3. Job title or position	Consultant dermatologists
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes ~~or No~~ A specialist in the treatment of people with this condition? Yes ~~or No~~ A specialist in the clinical evidence base for this condition or technology? Yes ~~or No~~ Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training, and research of dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of dermatology services across all service settings. It is funded by the activities of its members.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	None.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To achieve as close as possible to complete (cutaneous and psycho-social) clearance of nodular prurigo (NP) in patients with this condition.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	1. Reduction in physician global assessment (PGA) to half of the pre-treatment score. Or an absolute score of 1-2 out of a score of 4 and 2. Reduction in the DLQI (dermatology life quality index) of at least 4 points for inflammatory skin conditions and/or 3. Reduction in itch scores by 50%
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	In primary care (variably); then secondary care where patients are unresponsive, severely affected or request referral or cannot access certain medications within primary care.
9a. Are any clinical guidelines used in the	No; the BAD is developing a treatment guideline on this condition currently.

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Essentially, no. There are Japanese guidelines (*J Dermatol* 2021, 48; 414-31), but these are not internationally accredited. There is a general consensus to start with topical therapy, then phototherapy, then progress to systemics and biologics but there are also options for additional medications like antihistamines for itch and sleep or antidepressants which can be used alongside or at any point in the treatment pathway depending on the holistic needs of the patient. , 48; 414-31), but these are not internationally accredited. But there is a literature about treatments. The BAD is currently in the process of developing guidelines for the treatment of NP.
9c. What impact would the technology have on the current pathway of care?	It would make a very great difference to patients who have severe/recalcitrant disease. For these patients the technology has the potential (in those for whom it is effective) of being of very significant benefit.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes; dupilumab is already used to treat people with atopic dermatitis. There is a significant sub-population of patients with NP and concomitant eczema so this will be of particular benefit to these patients
10a. How does healthcare resource use differ between the technology and current care?	The technology is likely to be used in patients who have severe/recalcitrant disease in whom topical anti-inflammatory/phototherapy/systemic anti-inflammatory medications have been ineffective or contra-indicated.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In secondary care, specialist medical or psychodermatology clinics only.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The facilities for the initiation and monitoring of the technology already exist but adding the availability of the technology will add to the demand on these resources. However, it is likely that for those patients who respond to the technology, resource impact should diminish over time.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, there is more robust evidence here and here that this technology reduces pruritus, improves QoL and reduces severity of NP. The evidence that supports current treatment strategies such as phototherapy and systemic therapy such as ciclosporin, azathioprine and methotrexate is less robust (Qureshi *et al. J Am Acad Dermatol* 2019, 80: 756-64).
11a. Do you expect the technology to increase length of life more than current care?	There is not enough evidence for this. In certain circumstances, this may be possible (e.g. prevention of suicidal activity), but NP is not often a life-threatening disease.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, evidence from LIBERTY-PN PRIME and PRIME2.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	This depends. It should be easier, in the long run, for HCPs to monitor this technology compared with many anti-inflammatory systemic medications. It is also likely easier to *initiate* compared with many systemic anti-inflammatory medications. Most dermatology departments will have used this technology for other disease indications, and so will be familiar with its use. The main problem is usually access with updates needed for existing forms or systems to allow for prescribing of these medications.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This will depend on the NICE appraisal outcomes. HCPs will follow standard SmPC advice and will follow the rules around initiation of and monitoring for this technology as it has been applied to patients with atopic dermatitis.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes.
16a. Is the technology a 'step-change' in the management of the condition?	Yes.
16b. Does the use of the technology address any	Yes, in that there are very limited options for effective treatment of patients with severe of recalcitrant NP.

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Ocular surface disorders due to dupilumab therapy might affect the patient's QoL. There may be a considerable proportion of patients with NP who are atopic and may also have pre-existing atopic eye disease which may be asymptomatic prior to starting treatment with dupilumab. According to Fachler *et al.* JAAD 2021 and Akinlade *et al.* BJD 2019, it is often mild, unlikely to result in discontinuation of dupilumab and permanent sequelae is rare. The BAD, in collaboration with the Royal College of Ophthalmologists, is currently developing an expert consensus guidance paper on managing dupilumab-related ocular surface disorders.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Generally no, because there are currently no published guidelines on the management of people with NP and clinical practice is variable across the UK as a consequence. Clinical practice is also variable regarding scales used to assess and monitor treatment and how frequently it is used, but studies do seem to show efficacy but for small populations (Chiricozzi *et al.* 2020).
18a. If not, how could the results be extrapolated to the UK setting?	The BAD is currently developing guidelines on the management of people with NP, and these are likely to be published towards the end of this year. They include reference to the knowledge that the technology for this appraisal is being developed.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Sustained reduction in itch severity (WI-NRS), and consequently improvement in QoL and quality of sleep, is one of the most important outcomes followed by reduction in skin manifestations of NP especially at sites that are difficult to conceal. WI-NRS (worst itch numerical rating scale), sleep NRS and IGA (investigator global assessment) are measured in clinical trials.
18c. If surrogate outcome measures were used, do they adequately predict	This is untested, but clinical practice would indicate that these outcome measures are a reasonable assessment of long-term clinical outcomes.

long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to our knowledge.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not to our knowledge.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s)]	Not to our knowledge.
21. How do data on real-world experience compare with the trial data?	There is a scarcity of real-world data and publication bias towards case series, currently.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Erythema may be underestimated in those with more richly pigmented skin, hence the severity of their skin disease may be underestimated. Assessment of severity of itch, quality of sleep and health-related quality of life may be affected in those with disabilities such as visual hearing or cognitive impairment or language / communication difficulties
22b. Consider whether these issues are different from issues with current care and why.	This is similar to issues related to assessment of severity in other skin conditions, such as psoriasis.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• There is a significant unmet, clinical need for a safe, effective and approved medication in people with NP who have a poor response to or have co-morbidities that are contraindications to current available treatments. Treatments such as phototherapy require hospital attendance 2-3 times per week and the duration of use of some systemic immunomodulatory therapy such as ciclosporin may be limited due to adverse effects such as worsening renal function and elevation in blood pressure readings. • • • •

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Single Technology Appraisal
Dupilumab for treating prurigo nodularis [ID4054]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Prurigo Nodularis International
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	There is currently no external funding. The group has over 4,700 members.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information was gathered by putting questions directly to members, that consist of patients and carers.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	• Living with PN is life changing, the disease touches every aspect of patients lives. • 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. • Symptoms also get worse at night, which means patients are very sleep deprived and exhausted. • The symptoms are so severe that it often impacts the ability for many patients to work. This can have devastating economic implications for patients and their families. • It is also time consuming and expensive given how much time it takes to moisturise, apply creams and any prescribed treatment. • Given that the majority of dermatologists know nothing about PN or how to treat it, the diagnosis journey is very taxing on patients time and resources. It is also similar once a diagnosis has been achieved. Given the only treatment options are empirical (steroids – topical and oral, antihistamines, cancer treatments, immunosuppressants and steroid sparing agents), patients are subject to trying a myriad of empirical treatments, which is also very taxing on resources. • There is shame and social stigma attached to the disease, thereby making social interactions challenging. Aside from the discomfort, sleep deprivation and other issues outlined above, many patients become reclusive, shunning social interaction. Establishing and maintaining intimate relationships can also be a challenge, given the nature of the disease. • Carers report often feeling helpless as there is little they can do to help alleviate symptoms for patients.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	• It is difficult to find a dermatologist who is able to quickly diagnose the disease. Therefore, it can often take years to achieve a diagnosis. • As clinicians do not know or understand the disease, when patients present, they are often dismissed outright, told that it's all in their heads or to just stop scratching. • Once a diagnosis has been made there are no established care pathways. • There are no targeted treatments, only empirical treatments which often do little to nothing to help treat Prurigo Nodularis, while at the same time exposing patients to often quite dangerous side-effects, which can lead to patients developing other conditions, which they otherwise might not have during the course of their natural lives. Topical steroid treatments are particularly ineffective, yet clinicians continuously reach for these. • Patients can find themselves often going from one ineffective and dangerous drug to another, in the hope that one may help.
8. Is there an unmet need for patients with this condition?	There currently aren't any treatments designed specifically for this condition. As outlined and covered in previous answers. Patients are currently in a situation of trying one empirical treatment after another, often with little to no results, while being exposed to dangerous side effects and risk developing other conditions as a result of these empirical treatments. Furthermore, the lack of dedicated treatment options also means that the disease is left unchecked with the potential to destroy patients lives, as outlined in other answers.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The main advantage outlined by some of our members are: • A reduction in itch • Flattening of nodules Resulting in an ability to live a normal life.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	A few of the disadvantages outline by some of our members are: - Eyesight changes. - Diarrhoea - Vomiting - Microbial human mite infestation - Joint issues

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	N/A

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Even though achieving a diagnosis for this condition is a more general point, achieving a diagnosis of this condition can be challenging especially for patients of colour, as Dermatologists are often unable to recognise the condition on coloured skin, as most training text books lack representation. Therefore, if patients do not receive a timely and accurate diagnosis, patients of colour may be at a particular disadvantage and be unable to access the technology even if it were available.

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Nodular Prurigo or Prurigo Nodularis is a devastating, life changing disease. It has a deeply detrimental impact on all aspects of patients lives, including, physical, mental, emotional, financial and relationships. • For patients the route to 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, it is currently very much a lottery for patients that they may be lucky to be under the care of a clinician who is aware of the disease and the latest developments in care and treatment for this disease. • Once diagnosed patients do not have any dedicated treatments, there are only empirical treatments available. Patients must often go from trying one empirical treatment to the next, enduring often potentially dangerous and potent side effects for little to no benefit, in the hope that something will help and even when an empirical treatment helps, it's not clear why and may not necessarily help another patient. • The disease if not contained and treated with the appropriate agents (currently none available) 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.

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External Assessment Group Report
Dupilumab for treating moderate to severe prurigo nodularis

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Mark Corbett performed the critical appraisal of the clinical effectiveness evidence. Anqian Zhou performed the critical review of the economic analyses, conducted the EAG additional analyses, and contributed to the writing of Sections 4, 5 and 6 of the report. Sumayya Anwer contributed to the critical appraisal of the clinical effectiveness evidence. Ros Wade wrote the critique of the decision problem and contributed to the critical appraisal of the clinical effectiveness evidence. Tao Chen performed the critical review of the economic analyses and contributed to the writing of Section 4 of the report. Helen Fulbright wrote the search strategy sections. Laura Bojke provided advisory support for the critical review of the economic analyses and provided comments on the draft report. Alison Eastwood provided advice, commented on drafts of the report, takes overall responsibility for the clinical effectiveness sections and joint responsibility for the report as a whole. Claire Rothery performed the critical review of the economic analyses, drafted Sections 4, 5 and 6 of the report, led the overall economic analyses and takes joint responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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Figure 4 Markov trace showing the proportion of responders and non-responders to BSC alone over time..... 67

List of abbreviations

AD	Atopic dermatitis
AE	Adverse event
AESI	Adverse event of special interest
BSC	Best supportive care
CHE	Centre for Health Economics
CI	Confidence interval
CPRD	Clinical Practice Research Dataline
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
DAOSD	Dupilumab-associated ocular surface disease
DLQI	Dermatological Life Quality Index
EAG	External Assessment Group
EASI	Eczema Area and Severity Index
EMA	European Medicines Agency
EQ-5D	Standardised instrument for use as a measure of health outcome
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
FDA	Food and Drug Administration
GP	General practitioner
HADS (A/D)	Hospital Anxiety and Depression Scale (anxiety/depression subscale)
HCRU	Healthcare resource use
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IFSI	International Forum for the Study of Itch
IGA	Investigator Global Assessment
IGA PN (A/S)	Investigator Global Assessment for Prurigo Nodularis (activity/stage)
IgG4	Immunoglobulin G4
IL	Interleukin
IMP	Investigational medicinal product
ITC	Indirect treatment comparison
ITT	Intention to treat
LYG	Life years gained
MHRA	Medicines and Healthcare products Regulatory Agency

MI	Multiple imputation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRS	Numerical Rating Scale
OLE	Open-label extension
PAS	Patient Access Scheme
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PN	Prurigo nodularis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAE	Severe adverse event
SEE	Structured expert elicitation
SLR	Systematic literature review
SmPC	Summary of product characteristics
SNRI	Serotonin-norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
STEER	Structured expert elicitation resources
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
VAS	Visual Analogue Scale
WI-NRS	Worst-Itch Numeric Rating Scale
WOCF	Worst observation carried forward

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report, starting at Section 2.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID4054	Summary of issue	Report sections
1	Exclusion of antihistamines, oral steroids, immunosuppressive therapies and antidepressants as comparators	2.3
2	The best supportive care interventions used in the PRIME trials do not adequately reflect the interventions currently used in the NHS	3.2.1.1
3	Limited applicability of the PRIME trial populations to the NHS population	3.2.1.1
4	[redacted]	3.2.2.4
5	Model structure for BSC	4.2.2.1
6	Response criteria	4.2.6.1
7	Long-term treatment effect and response waning	4.2.6.2
8	Utility values for non-responders	4.2.8.3 and 4.2.8.4
9	Resource use	4.2.9.1

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are: (i) treatment response rates are based on the combined response criterion of WI-NRS improvement ⩾4 and IGA-PN-S score of 0 or 1 from baseline to week 24 rather than the combined criterion of WI-NRS improvement ⩾4 and IGA-PN-S reduction ⩾1 because the former is consistent with the key endpoints of the PRIME trials; (ii) all-cause discontinuation rate for BSC is set to 0%, with response waning on BSC included, whereas the company's preferred assumptions include *both* an all-cause annual treatment discontinuation rate (that includes loss of treatment response) and a

probability of sustained response per year; (iii) pooled (across treatment arms) utility value at week 24 is used for non-responders rather than a treatment arm-specific utility value for non-responders; (iv) the utility values for non-responders (separated by those who did not respond to treatment by week 24 and those who responded to treatment by week 24 but subsequently discontinued treatment at a later time point) are assumed to hold constant only for the first six months after treatment discontinuation and then rebound to baseline utility, whereas the company assumes that the utility values for dupilumab plus BSC non-responders when they move to BSC remain higher than the utility values for BSC, even after 5+ years loss of treatment response.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients who achieve response to treatment because response is associated with improved health-related quality of life.
- Improved health-related quality of life for non-responders to treatment compared to BSC (comparator).
- There are no survival benefits associated with treatment.

Overall, the technology is modelled to affect costs by:

- Greater acquisition costs compared to the comparator.
- Increasing the proportion of patients who achieve response to treatment because response is associated with lower disease management and rescue medication costs.
- Higher adverse event costs compared to the comparator.

The modelling assumptions that have the greatest effect on the ICER are:

- The annual discontinuation rate or response waning assumptions (loss of response) over time for BSC.
- The use of treatment arm-specific utility values for non-responders to treatment.
- The extrapolation of utility values for non-responders over time after treatment discontinuation.
- The response criterion used to assess response to treatment.

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Exclusion of antihistamines, oral steroids, immunosuppressive therapies and antidepressants as comparators

Report section	2.3
Description of issue and why the EAG has identified it as important	Many of the treatments currently used to treat PN in the NHS (and listed in the final scope) were not considered appropriate comparators in the company's submission. These omissions have implications for the relative efficacy data (effect sizes; see Issue 2) and may also be important since there has been little consideration of issues such as plausible treatment sequences (given dupilumab's license), different discontinuation rates and different costs across the various comparator treatments.
What alternative approach has the EAG suggested?	To help inform the possible benefits of these treatments the EAG identified and critiqued two studies of methotrexate/ciclosporin efficacy which were not included in the company's systematic review.
What is the expected effect on the cost-effectiveness estimates?	The EAG is unable to predict the expected effect on the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	See Issue 2

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 The best supportive care interventions used in the PRIME trials do not adequately reflect the interventions currently used in the NHS

Report section	3.2.1.1
Description of issue and why the EAG has identified it as important	In the PRIME trials, the availability and use of BSC treatments was very limited because many treatments were prohibited during the trials. Consequently, the use of the following components of BSC are all substantially below what would be expected in an NHS PN cohort: methotrexate, ciclosporin, systemic corticosteroids, antihistamines, high or super potent TCS and occlusion of TCS. To inform the possible benefits of BSC the EAG identified two studies of methotrexate/ciclosporin efficacy which were not included in the company's systematic review. Had the PRIME trials been done in an NHS setting, greater use of several BSC treatments would have been expected in the trial placebo arms, than in the dupilumab arms. This would have likely resulted in reduced dupilumab effect estimates (when compared to the PRIME trial results presented in the CS).
What alternative approach has the EAG suggested?	There is no viable alternative approach using the data currently available.
What is the expected effect on the cost-effectiveness estimates?	Higher response rates associated with BSC may be expected in practice compared to those observed in the trials. Therefore, the EAG expects the company's base case ICER of £27,010/QALY to increase because the company's base case assumptions use a very high annual discontinuation rate for BSC and a low probability of sustaining response on BSC over time, which means that the predicted response rate for BSC diminishes very rapidly (incurring lower utility and higher resource use and costs associated with non-response to treatment) compared to dupilumab plus BSC.
What additional evidence or analyses might help to resolve this key issue?	This issue can only be fully resolved with results from a trial which uses best supportive care which adequately reflects NHS BSC. However, there are no prior nor ongoing trials which would produce such results.

Issue 3 Limited applicability of the PRIME trial populations to the NHS population

Report section	3.2.1.1
Description of issue and why the EAG has identified it as important	Only [redacted] of the PRIME cohort had previously used methotrexate – a key treatment used in the NHS population. A largely methotrexate-naive trial population may be easier to treat (i.e. more likely to achieve responses to the key trial outcomes) than

	the more methotrexate-experienced population likely to treated with dupilumab in the NHS. Also, in both PRIME trials, participants on stable regimens of high potency or super potent TCS at screening were to decrease potency to medium potency; the EAG could not find data on how many patients dropped their dose in this way. The magnitude of the responses in these patients may be greater than would have been seen had the trials allowed the continuation of stable regimens of high/super potent TCS (as the disease may have been a little better controlled in these patients).
What alternative approach has the EAG suggested?	There is no viable alternative approach using the data currently available.
What is the expected effect on the cost-effectiveness estimates?	The treatment response rate with BSC would be expected to increase, with associated increase in the ICER, however, the magnitude is uncertain.
What additional evidence or analyses might help to resolve this key issue?	This issue can only be fully resolved with results from a trial which recruits a population which adequately reflects the one likely to be seen in the NHS.

Issue 4 [redacted]

Report section	3.2.2.4
Description of issue and why the EAG has identified it as important	[redacted]
What alternative approach has the EAG suggested?	[redacted]
What is the expected effect on the cost-effectiveness estimates?	[redacted]
What additional evidence or analyses might help to resolve this key issue?	This issue can only be fully resolved with results from a trial which recruits a population which adequately reflects the one likely to be seen in the NHS. Future studies should also consider if weight-based dosing/dose escalation may alter the efficacy of dupilumab in higher weight patients (e.g. >90kg)

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 5 Model structure for BSC

Report section	Section 4.2.2.1. Item 1; Item 2.
Description of issue and why the EAG has identified it as important	In the company's model, BSC responders are separated from BSC non-responders because health-related quality of life utility values and costs differ by response status. However, the creation of separate treatment states for BSC responders and non-responders means that an additional assumption about long-term discontinuation on BSC for responders is required (and this discontinuation rate is a key driver of the cost-effectiveness results), even though patients are not discontinuing BSC treatment, as this remains the background treatment for all patients. Furthermore, the model applies separate utility values for dupilumab plus BSC non-responders (who continue on BSC only) from BSC non-responders, while costs for disease management and rescue therapy medications are assumed to be the same for all non-responders. This creates inconsistencies in the way that non-responders are modelled over time. Given the fact that treatment with BSC is defined the same under both treatment options, it would seem reasonable to assume that dupilumab non-responders who continue on BSC only would be expected to have the same utility values and costs associated with BSC non-responders.
What alternative approach has the EAG suggested?	A BSC treatment state, with utility values and costs weighted by the likelihood of response to BSC over time, is likely to better reflect fluctuations in response to standard treatment without dupilumab (e.g., from the use of systemic therapies). As a comparator treatment, patients receiving BSC can incur the efficacy benefits of placebo from the trials but weighted by the percentage of responders and non-responders.
What is the expected effect on the cost-effectiveness estimates?	The EAG is unable to predict the expected effect on the cost-effectiveness estimates. However, the EAG conducted two scenarios to assess the impact on cost-effectiveness when the response rate for BSC at week 24 is held constant over time: • EAG Scenario 5, where the response rate from the trials is held constant over time, shows that the ICER increases from the company's base case ICER of £27,010/QALY to £106,039/QALY. • EAG Scenario 6, where 25% of the response rate for BSC is held constant over time, shows that the ICER increases from £27,010/QALY to £27,816/QALY.
What additional evidence or analyses might help to resolve this key issue?	Ideally the model would discount any placebo effect from the results of the trials and then just model the true effect of BSC as the background treatment for all patients, including dupilumab non-responders.

Issue 6 Response criteria

Report section	Section 4.2.6.1. Item 5; Item 6.
Description of issue and why the EAG has identified it as important	The efficacy response criteria are used to define which patients are responders to treatment at week 24. The response criterion used in the model is the composite of WI-NRS improvement ⩾4 and IGA-PN-S reduction ⩾1 from baseline to week 24. However, IGA-PN-S reduction ≥1 was not considered a key primary or secondary outcome measure in the PRIME2 and PRIME trials, whereas the proportion of participants with IGA PN-S 0 or 1 score at week 24 was considered a key outcome. The EAG also considers an improvement in the DLQI to be important when considering adequate response to dupilumab in PN because WI-NRS and IGA-PN-S are not routinely used to assess response in NHS practice.
What alternative approach has the EAG suggested?	For consistency with the endpoints used in the trial, the EAG considers it more appropriate to use IGA PN-S 0 or 1 score in the composite response criterion used in the model, rather than IGA-PN-S reduction ≥1. The EAG considers an improvement in the DLQI to be important when considering adequate response to dupilumab in PN.
What is the expected effect on the cost-effectiveness estimates?	The EAG Scenario 1 demonstrates the impact of the alternative response criterion of WI-NRS improvement ⩾4 and IGA-PN-S score of 0 or 1 from baseline to week 24 on the cost-effectiveness results: • EAG Scenario 1 shows that the ICER decreases from the company's base case ICER of £27,010/QALY to £25,279/QALY. The reason for the decrease in the ICER is that although the response rate to dupilumab plus BSC is lower under the alternative response criterion, the non-responders to dupilumab plus BSC are benefiting from a larger utility difference associated with dupilumab plus BSC non-responders compared to BSC non-responders over time, while the total costs associated with dupilumab plus BSC falls due to lower drug acquisition costs associated with non-response. Importantly, this demonstrates that the relative difference in the response rates observed in the trials for dupilumab plus BSC compared to BSC alone at week 24 for the different response criteria is less important for the cost-effectiveness of dupilumab plus BSC in the company's model because the company assumes a higher utility value for dupilumab plus BSC non-responders compared to BSC non-responders (even though all non-responders receive BSC only), whilst also assuming that the response rate for BSC rapidly falls to 0%.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is required for the response criterion of WI-NRS improvement ⩾4 and IGA-PN-S score of 0 or 1 from baseline to week 24. Additional evidence on the response rates by treatment arm for at least a 4-point reduction in the DLQI, in line with that used to define adequate response in the analogous disease area of AD, may be helpful.

Issue 7 Long-term treatment effect and response waning

Report section	Section 4.2.6.2. Item 7; Item 8; Item 9.
Description of issue and why the EAG has identified it as important	The company assumes that patients who achieve response at 24-weeks persist on treatment until discontinuation due to loss of response, adverse events or patient/clinician preference. The model includes both an all-cause annual treatment discontinuation rate for responders to dupilumab plus BSC and BSC (even though BSC patients do not discontinue treatment) and a probability of sustained response per year; both of which are implemented as a transition probability [additively] from the 'Response' to 'No response' treatment state in the model. The annual treatment discontinuation rates and probabilities of sustained response over time for both dupilumab plus BSC and BSC alone are also highly uncertain due to short trial follow-up and limited evidence.
What alternative approach has the EAG suggested?	The EAG does not consider it appropriate to include both an all-cause annual treatment discontinuation rate (that includes loss of response over time) and a probability of sustained response per year, for responders in the model. If the main purpose of the response waning assumptions is to account for the high response rates seen in the placebo arm of the trials due to improved adherence to BSC treatment that is unlikely to be sustainable for a prolonged period of time outside a clinical trial setting, then the EAG considers that any benefit from improved adherence would be expected to be applied equally to both the treatment arms of the clinical trials, which should not affect how the treatments perform relative to one another.
What is the expected effect on the cost-effectiveness estimates?	The implications of a very high annual discontinuation rate for BSC and 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, with everyone on BSC assumed to be non-responders very quickly (incurring lower utility and higher resource use and costs associated with non-response to treatment). The EAG scenarios demonstrate the impact on the cost-effectiveness results: • EAG Scenario 2, where the all-cause discontinuation rate for BSC is set to 0% (includes response waning on BSC), increases the ICER from £27,010/QALY to £29,026/QALY. • EAG Scenario 3, where the response waning assumptions are switched off for both treatment arms (includes all-cause discontinuation rate), increases the ICER from £27,010/QALY to £28,822/QALY.
What additional evidence or analyses might help to resolve this key issue?	Evidence on the long-term treatment effect and discontinuation rates associated with dupilumab plus BSC and BSC alone.

Issue 8 Utility values for non-responders

Report section	Section 4.2.8.3. Item 10. Section 4.2.8.4. Item 11; Item 12.
Description of issue and why the EAG has identified it as important	Treatment arm-specific utility values are used for non-responders in the model. However, the EAG notes that there is a much larger difference in utility weights between treatment arms in non-responders at week 24 (i.e., in those who did not respond to treatment by week 24 and receive BSC only) compared to the difference between treatment arms in responders to treatment at week 24. The EAG does not consider it appropriate to apply separate utility values by treatment arm for non-responders because all non-responders receive BSC only in the model, and any treatment effect is expected to diminish upon discontinuation of treatment. The utility values for non-responders are also adjusted down over time based on the results of a structured expert elicitation (SEE). The EAG has concerns about the credibility of the results of the SEE and identified a number of inconsistencies in the approach used by the company to adjust the utility values over time.
What alternative approach has the EAG suggested?	The EAG considers that the pooled (across treatment arms) week 24 utility value for non-responders from the trials would be more appropriate for all non-responders in the model at week 24 (irrespective of treatment arm) because these patients have not responded to treatment and all non-responders receive BSC only. The EAG considers it appropriate to assume that the utility values for non-responders hold constant only for the first six months after treatment discontinuation and then rebound to baseline utility because the [redacted] The EAG also considers it important to distinguish a difference in utility values between those who did not respond to treatment by week 24 and those who responded by week 24 but subsequently discontinued treatment and became a non-responder.
What is the expected effect on the cost-effectiveness estimates?	The EAG preferred assumptions have an impact on the cost-effectiveness results: • EAG Scenario 7, which uses the pooled week 24 utility value for non-responders, increases the ICER from £27,010/QALY to £29,176/QALY. • EAG Scenario 12, where the 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, increases the ICER from £27,010/QALY to £32,763/QALY.
What additional evidence or analyses might help to resolve this key issue?	Evidence on health-related quality of life upon treatment discontinuation.

Issue 9 Resource use

Report section	Section 4.2.9.1. Item 13; Item 14; Item 15.
Description of issue and why the EAG has identified it as important	Three issues were identified in resource use: (i) The company used the frequency of rescue medication use from the PRIME trials over a 24-week period as a proxy for long-term use of rescue therapies. However, given the EAG's concern about the limited generalisability of the PRIME trial populations to the NHS population, and the greater adherence to treatments in the protocol-driven trial setting, the EAG believes it is unlikely that the frequency and type of rescue medications used in the trials are a good proxy for long-term use in the NHS. (ii) The company used frequency of inpatient hospitalisations for dermatology in the model, which is associated with two times higher frequency compared to the inpatient hospitalisation for PN. The EAG considers that the frequency of hospitalisations may be overestimated in the model as hospitalisations for PN are rare. (iii) The adverse event costs for dupilumab may be underestimated if there are additional monitoring costs associated with severe ocular side effects.
What alternative approach has the EAG suggested?	For issue (ii), the EAG considers it is more relevant to use the PN-specific inpatient hospitalisation frequency in the model.
What is the expected effect on the cost-effectiveness estimates?	The expected effect of these issues on the cost-effectiveness results is minimal because the additional costs of dupilumab plus BSC compared to BSC alone are driven largely by the drug acquisition costs of dupilumab, with a small proportion of this cost offset by lower disease management costs associated with a greater number of responders to dupilumab plus BSC versus BSC alone. Adverse event and rescue medication costs represent about 1% of the total incremental cost.
What additional evidence or analyses might help to resolve this key issue?	Evidence on the frequency and type of rescue medications used in the NHS, frequency of hospitalisations in PN and frequency of severe ocular side effects associated with dupilumab in PN patients.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 summarises the EAG's preferred assumptions and resulting ICER. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.

Table 2 Summary of EAG's preferred assumptions and resulting ICER

Scenario	**Incremental cost**	**Incremental QALYs**	**ICER (change from company base case)**
Company's base case	[redacted]	[redacted]	£27,010
EAG Scenario 1: Response criteria of WI-NRS improvement ≥4 and IGA-PN-S score of 0 or 1 from baseline to week 24	[redacted]	[redacted]	£25,279 (-£1,731)
EAG Scenario 2: All-cause discontinuation rate for BSC set to 0% (includes response waning on BSC)	[redacted]	[redacted]	£29,026 (+£2,016)
EAG Scenario 7: Same utility value by treatment arm for non-responders based on week 24 pooled value for non-responders	[redacted]	[redacted]	£29,176 (+£2,166)
EAG Scenario 12: 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. A distinction in utilities is also made between 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-responder in the model.	[redacted]	[redacted]	£32,763 (+£5,753)
EAG's preferred base case EAG Scenarios 1 + 2 + 7 + 12	[redacted]	[redacted]	£37,291 (+£10,281)

Abbreviations: BSC: best supportive care; EAG: external assessment group; QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report presents a critique of the company's submission (CS) to NICE from Sanofi on the clinical effectiveness and cost effectiveness of dupilumab (Dupixent®) for treating moderate-to-severe prurigo nodularis (PN), also known as nodular prurigo.

Dupilumab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signalling. European Medicines Agency (EMA) marketing authorisation approval for dupilumab in adults with moderate to severe PN was received on 12 December 2022.[1] UK marketing approval was expected from the Medicines and Healthcare products Regulatory Agency (MHRA) by [redacted]. The MHRA Summary of Product Characteristics (SmPC) for dupilumab 300 mg includes PN as a therapeutic indication.[2]

2.2 Background

PN is a rare, chronic condition that is difficult to treat and there are no established treatment guidelines. Pruritis (itch) is the most burdensome symptom and has a major impact on quality of life. The estimated prevalence of PN in England is 3.27 per 10,000 (95% confidence interval [CI]: 3.15 to 3.40), using an analysis of the Clinical Practice Research Dataline (CPRD) Aurum database, which contains primary care data from over 40 million patients in the UK. The proportion of patients with moderate to severe disease and inadequately controlled PN is estimated to be 26.8% of the PN adult population, therefore, the company estimate that there are currently 14,750 adult patients with PN and 3,953 adult patients with moderate to severe and inadequately controlled PN in England.

There is no standard disease severity measure for PN routinely used in clinical practice; the CS describes the Investigator's Global Assessment for Prurigo Nodularis – Stage (IGA PN-S) scale, which classifies the extent of disease on a five-point scale based on lesion count, ranging from 0 (clear; no nodules) to 4 (severe; >100 nodules). The intensity of pruritis is scored from 0 (no pruritis) to 10; a score of ≥9 is very severe pruritis. The EAG's clinical advisers stated that the clinical pathway of care for people with PN presented in the CS appears appropriate (CS section B.1.3.2). The International Forum for the Study of Itch (IFSI) treatment ladder for chronic prurigo presented in the CS (Figure 4) appears generally reflective of treatment approaches in the UK, although often patients move directly from Step 1 to Step 3 and there is a certain amount of "trial and error" used in the treatment choices.

The CS states that dupilumab will be indicated for the treatment of adults with moderate-to-severe PN who are candidates for systemic therapy. The clinical experts who participated in the company's

December 2022 advisory board advised positioning dupilumab where off-label systemics are currently used (which concurs with the anticipated marketing authorisation) or possibly before "due to the lack of evidence for these agents in PN compared to psoriasis and atopic dermatitis". The CS stated that the most appropriate comparator for dupilumab is best supportive care (BSC), defined as a combination of emollients, mild-to-moderate potency topical corticosteroids/topical calcineurin inhibitors (TCS/TCIs) and rescue therapy, i.e. the company chose to position dupilumab before off-label systemics, rather than where off-label systemics are currently used. This issue is discussed further in Section 3.2.1.1.

Whilst there are currently no approved targeted systemic treatments for PN, other therapies being investigated for use in moderate-to-severe PN include nemolizumab, vixarelimab, nalbuphine, abrocitinib, and INCB054707.[3] Additionally, a phase I trial investigating barzolvolimab is in progress.[3]

2.3 Critique of company's definition of decision problem

Table 1 of the CS presents the decision problem, including a description of the final scope issued by NICE, the decision problem addressed within the submission and the rationale for any differences between the two. This information, along with the EAG comments on the rationale provided, is presented in Table 3 below.

EAG comments

Comparators

The BSC therapies used in the PRIME2 and PRIME trials (emollients and low to medium potency TCS/TCIs) are much more conservative than those commonly used in NHS practice; BSC is likely to include one or more of: a high- or super-potent topical corticosteroid, a systemic immunosuppressant, most commonly methotrexate or ciclosporin, an antidepressant, antihistamines, and oral steroids. In the dupilumab PRIME trials the following interventions were prohibited: systemic immunosuppressants, antihistamines (used for treating atopic dermatitis or PN), oral steroids and occlusion of nodules treated with TCS. High- or super-potent TCS were only allowed as rescue medications and antidepressants were only allowed in patients who were taking stable doses before randomisation. Therefore, patients in the PRIME trials received a much lower level of BSC than patients in NHS practice. Although the company correctly states that there is a lack of randomised controlled trial (RCT) evidence to support the efficacy of antihistamines, oral steroids, immunosuppressive therapies and antidepressants, these nevertheless collectively form the BSC currently used in the NHS and the EAG does not agree with their exclusion as comparators.

Outcomes

The EAG does not agree with the company's justification for excluding disease-free period/maintenance of remission and time to relapse/prevention of relapse outcomes, as these outcomes are important to patients. However, the lack of longer-term data (beyond 24 weeks of treatment) restricts any meaningful analysis of these outcomes in the included trials.

Table 3 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with moderate to severe PN that had inadequate response or intolerance to existing topical treatments.	As per final scope.	Not applicable.	The population described in the CS is broadly in line with the NICE scope, although there were some important differences in population characteristics between the PRIME trials and the NHS population (see Section 3.2.1.1). The PRIME trial included patients from 63 centres in eight countries/regions. The PRIME2 trial included patients from 57 centres in eleven countries/regions. Only three patients (from one trial site) were from the UK. However, as a rare condition, there are limited data to indicate whether differences in race/ethnicity would lead to differences in treatment response.
Intervention	Dupilumab in combination with topical emollients, TCSs and TCIs.	As per final scope.	Not applicable.	The intervention described in the CS is in line with the NICE scope.
Comparator(s)	Established clinical management without dupilumab, including: • Topical emollients • TCSs • TCIs • Antihistamines • Oral steroids • Phototherapy	The company considers the following comparators to be the most relevant: • Topical emollients • TCSs • TCIs	There is a lack of RCT evidence to support the efficacy of antihistamines, oral steroids, phototherapy, immunosuppressive therapies and antidepressants in treatment of PN. Phototherapy is used earlier in the treatment pathway and so cannot	The 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.

	• Immunosuppressive therapies (azathioprine, ciclosporin, methotrexate or thalidomide) • Antidepressants including SSRIs and SNRIs.		be regarded as a direct comparator. Moreover, clinical experts in the UK who participated in the December 2022 advisory board conducted by Sanofi advised positioning dupilumab where off-label systemics are currently used to provide patients with the most effective treatment as early as possible while minimising potential side effects.[4]	
Outcomes	The outcome measures to be considered include: • Measures of disease severity • Measures of symptom control including improvement in itch • Disease-free period/ maintenance of remission • Time to relapse/prevention of relapse • Adverse effects of treatment • HRQoL.	Outcomes measured in PRIME2 and PRIME: • Measures of disease severity • Measures of symptom control including improvement in itch • Adverse effects of treatment • HRQoL.	Disease-free period/ maintenance of remission and time to relapse/prevention of relapse outcomes were included in the scope to align with a previous submission to NICE for AD [TA534];[5] however, these outcomes are not relevant to PN.	The EAG does not agree with the company's justification for excluding disease-free period/maintenance of remission and time to relapse/prevention of relapse outcomes, as these are important outcomes to patients. In response to the EAG's clarification questions the company stated that the clinical trials were not designed or powered sufficiently to provide results for these outcomes. The EAG accepts that the lack of longer-term data (beyond 24 weeks) restricts any meaningful analysis of these outcomes in the included trials. The CS reports results for IGA PN-S, IGA PN-A, WI-NRS, skin pain-NRS,

				DLQI, HADS, sleep NRS and adverse effects. Other outcomes assessed in the PRIME2 and PRIME trials, but not reported in the submission, were EQ-5D-5L, EQ-5D VAS, PGIC and PGIS; these results were provided by the company in response to the EAG's clarification questions. Whilst the primary endpoint of PRIME2 and PRIME (WI-NRS improvement ≥4 points) is not routinely used in clinical practice, this is a reasonable primary outcome measure that is relevant to patients and the 4-point improvement represents a clinically-significant improvement.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent	The reference case has been adhered to.	Not applicable – in line with final NICE scope	In line with NICE scope.

	treatment technologies will be taken into account.			

Abbreviations: AD: atopic dermatitis; CS: company submission; DLQI: dermatology life quality index; EAG: External Assessment Group; EQ-5D-5L: EuroQol 5-dimensions 5-levels; EQ-5D VAS: EuroQol 5-dimensions visual analogue scale; HADS: hospital anxiety and depression scale; HRQoL: health-related quality of life; IGA PN-A: Investigator's Global Assessment of Prurigo Nodularis – Activity; IGA PN-S: Investigator's Global Assessment for Prurigo Nodularis – Stage; NICE: National Institute for Health and Care Excellence; NRS: numeric rating scale; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PN: prurigo nodularis; RCT: randomised controlled trial; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCIs: topical calcineurin inhibitors; TCSs: topical corticosteroids; WI-NRS: worst-itch numeric rating scale.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify all relevant clinical evidence relating to the efficacy and safety of treatments for adults with PN. Details of the SLR are reported in Appendix D of the CS.

3.1.1 Searches

The SLR included searches to identify clinical evidence on dupilumab and relevant key comparators in the treatment of adult patients with PN. A description of the searches and the search strategies were included in CS Appendix D (pages 8 to 14). The EAG appraisal of the literature searching is presented in Appendix 1. In response to the EAG's clarification questions, a further document was provided by the company, which included additional strategies and corrections to errors identified by the EAG. The EAG does not have access to Evidence Based Medicine (EBM) Reviews and therefore cannot fully scrutinise these strategies.

3.1.2 Inclusion criteria

The eligibility criteria used to select studies for inclusion in the SLR of clinical effectiveness evidence were presented in Table 4 in Appendix D of the CS. The eligibility criteria were broader than the decision problem addressed in the CS. The population was adult patients with PN, with no restriction to 'moderate to severe disease that had inadequate response or intolerance to existing topical treatments'. The interventions of interest included any pharmacological intervention for PN, comparators were placebo or any other treatment, and a broader range of outcomes of interest were listed (any efficacy, safety, quality of life or patient reported outcomes). Only studies reported in English were eligible for inclusion.

Study selection was undertaken independently by two reviewers, with disagreements resolved by discussion or referral to a third senior researcher, minimising the possibility of errors or bias affecting the study selection process. The EAG reviewed the table of publications excluded at the full text review stage (Table 12 in Appendix D of the CS) and identified a study which appears to have been incorrectly excluded.[6] In response to a clarification question the company changed its reason for exclusion from "study design not of interest" to "No intervention". However, this study reports efficacy data for 74 patients taking immunosuppressants (methotrexate or ciclosporin). Moreover, the EAG identified a study of 39 patients who took methotrexate which the company did not identify in the SLR presented in the submission.[7] Both of these studies are discussed in Section 3.3.

The SLR identified seven unique randomised controlled trials (RCTs) and 21 unique non-RCTs. Supplementary searches of Clinicaltrials.gov identified two additional RCTs; PRIME2 and PRIME, which are not available as peer-reviewed manuscripts. The CS focussed on the only two RCTs assessing dupilumab; PRIME2 and PRIME. Study characteristics and results of the other included RCTs and non-RCTs (including three small non-RCTs of dupilumab)[8-10] are presented in Appendix D (Tables 5 to 11).

3.1.3 Critique of data extraction

Data extraction methods were not reported, therefore it is unclear whether processes to reduce the potential for errors or bias were used. Information on the design and methods of PRIME2 and PRIME were presented in the CS, along with baseline characteristics of participants in both studies and the pooled intention to treat (ITT) population (Section B.2.3). Results of PRIME2, PRIME and the pooled ITT analysis were presented in Section B.2.6 of the CS, with subgroup analysis results presented in Section B.2.7. However, some important information was missing from the CS and the clinical study reports (CSRs), which the EAG requested at the clarification stage, such as additional information on the number of patients in the analyses at different timepoints, the number of patients represented by imputed data and reasons for missing data, details of rescue treatments or prohibited medications given to patients who were non-responders, details of all best supportive care used by patients in each treatment arm and results at week 36 (end of study) after the 12-week post-treatment follow-up period. This additional information was provided by the company in response to the EAG's clarification questions.

3.1.4 Quality assessment

The quality assessment of the PRIME2 and PRIME trials is presented in Table 11 of the CS, with further details presented in Appendix D (Table 13). The quality assessment criteria were appropriate, though the process details were not reported; it is therefore unclear whether processes to reduce the potential for errors or bias were used. There does not appear to be any assessment of the quality of other studies included in the systematic review. The PRIME2 and PRIME trials appear to have been well conducted with respect to internal validity, though there was an imbalance of dropouts between treatment groups, with significantly more patients dropping out of the placebo arm of both trials, primarily due to lack of treatment efficacy. In addition, there were some imbalances in participant baseline characteristics between treatment groups, particularly in the PRIME trial, although the EAG's clinical advisers were not concerned that there were any obvious clinically relevant differences between treatment groups. No formal assessment of external validity or applicability to the NHS setting was made. In a clarification question (A17), the EAG asked the company to comment on the applicability (to the NHS) of the best supportive care interventions given to patients in the PRIME trials. The company acknowledged that in the NHS topical steroids are usually high potency or else

high potency under occlusion and that methotrexate is used off-label in clinical practice. A critique of the applicability of the PRIME trial results to the NHS setting is provided in Section 3.2.1.1.

3.1.5 Evidence synthesis

Results from PRIME2 and PRIME were pooled as part of a prespecified protocol to increase the statistical power of efficacy and safety analyses. Pooled efficacy results from PRIME2 and PRIME are presented in the CS (pooled ITT analysis). The CS states that, while targeted systemic therapies are currently being investigated and the standardisation of efficacy endpoints is ongoing, indirect and mixed treatment comparisons were not considered feasible at this time to compare dupilumab against the comparators listed in the scope of the submission.

EAG comments

Although the SLR appears to have been mostly well conducted the EAG has concerns about relevant comparator studies not being identified or included (see Section 3.3) and the lack of consideration of the applicability of the PRIME trial results to NHS practice (see Section 3.2.1.1).

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The company's efficacy and safety data were based on the results of two placebo-controlled phase III RCTs of dupilumab: PRIME and PRIME2, which were also pooled as part of a prespecified analysis. In both PRIME trials patients are treated with either dupilumab plus best supportive care (BSC) or placebo plus BSC.

3.2.1 Design and methods of the PRIME and PRIME2 trials

The two PRIME trials had very similar designs and 24-week treatment periods. The PRIME study was conducted at 63 centres in eight countries/regions worldwide (US, Argentina, Mexico, Mainland China, Japan, Russian Federation, Republic of Korea and France). The PRIME2 study was conducted at 57 centres in 11 countries/regions worldwide (Canada, Chile, France, Hungary, Italy, Portugal, Republic of Korea, Spain, Taiwan, UK and US). One trial site, which enrolled three patients, was located in the UK. Eligibility criteria were reported in Table 5 and Appendix M1 of the CS.

The EAG's clinical advisers thought that the criterion that patients must have failed treatment with a two-week course of medium-to-super potent TCS (or when TCS was not medically advisable) was not reflective of practice, where patients would be given at least 4 weeks to respond to TCS (and probably longer, bearing in mind that other treatments - such as dupilumab - may take up to 24 weeks to reach full effectiveness). However, the EAG's advisers added that although they would have liked to have seen the trials recruit patients who had demonstrated an inadequate response to a more prolonged

exposure to a TCS, they thought it was likely that patients who have moderate-to-severe PN (≥20 lesions) would not respond adequately to a longer course.

Study design details were reported in section B.2.3.1 of the CS. The study protocol for PRIME was amended to make the proportion of patients with WI-NRS ≥4 from baseline to week 24 the primary endpoint because PRIME2 results became available while PRIME was still blinded, indicating that the effect of dupilumab continued to improve after week 12. The trial outcomes are appropriate for UK practice, although results for the Dermatology Life Quality Index (DLQI) were presented only as change from baseline (i.e. no data were available on how many patients achieved at least a 4-point reduction in DLQI).

In the company's primary analysis, patients were imputed as non-responders for binary outcomes if they received prohibited medications (such as immunosuppressants), rescue treatments, or if they had missing data. Continuous outcomes were analysed using an analysis of covariance method. After a patient received a rescue treatment, efficacy data were set to be missing and imputed using worst observation carried forward (WOCF). Patients who had missing data after discontinuing for a lack of efficacy were imputed using WOCF, and missing data for patients who discontinued for reasons other than a lack of efficacy were imputed using multiple imputation (MI).

In addition to the primary analysis, the company conducted two supplementary analyses using different imputation methods. In the 'as-observed' analysis, data for all patients who discontinued would be included as long as they had a measurement reported at week 12/week 24. If there was no measurement at the time-point of interest, patients were considered non-responders. In the 'hybrid' analysis, a hybrid method of WOCF and MI was used for patients who discontinued.

No long-term follow-up data on trial treatment efficacy were collected in either trial as participants stopped taking trial treatments at 24 weeks. Patients could then begin a 12-week post-intervention phase to observe the effect on outcomes of stopping treatment.

3.2.1.1 Critical appraisal of the PRIME studies

The EAG concurs with the company's assessment (Table 13 of the CS appendices) that the PRIME trials had a low risk of bias (i.e. they were internally valid).

The CS did not discuss how externally valid the trials were, or, more specifically, how applicable the results were to the NHS setting. The EAG noted key issues with both the population and best supportive care therapies used in the PRIME trials.

Population

Age and weight

The mean age of the pooled trial cohort was just under 50 years, whereas in practice the EAG's advisers thought the average age for patients with moderate-to-severe disease would be closer to 60 years. The EAG's advisers thought this might affect the incidence of comorbidity and potentially treatment emergent adverse event profiles. The younger age might also influence weight; the mean weight of the pooled trial cohort was around 74kg, with around 17% of patients weighing over 90kg. The EAG's advisers would expect higher figures in an NHS population. This is important as weight may be an effect modifier of dupilumab, based on the company's subgroup analyses (see Section 3.2.2.4).

Use of prior treatments

Only [redacted] of the PRIME cohort had previously used methotrexate – a key treatment used in the NHS population. A largely methotrexate-naive trial population may be easier to treat (i.e. more likely to achieve responses to the key trial outcomes) than the more methotrexate-experienced population likely to be seen in the NHS. Although the company presented a subgroup analysis based on "*history of use of systemic immunosuppressant*", which showed no difference in effect, most of the patients who had such a history had not taken methotrexate. The results of this subgroup analysis are also difficult to interpret since it is unknown how many patients failed to achieve a response to a prior systemic immunosuppressant, or lost their response, versus those who were achieving some response but stopped taking their systemic immunosuppressant to become eligible for entry into one of the PRIME trials. The former would be expected to be more difficult to treat than the latter.

In both PRIME trials,

[redacted]. Depending on the number of patients involved, this restriction may be a concern because participants who

[redacted]

Best supportive care

For the PRIME trial results to be considered applicable to the NHS setting and reliable for use in the cost-effectiveness modelling, it is important that the BSC used in the PRIME trials broadly reflects the interventions currently used in the NHS. However, as detailed in Section 2, the company excluded many therapies from its submission. These exclusions largely reflect the use of BSC in the PRIME trials, where many therapies were prohibited. Of note, the EAG's advisers indicated that in the NHS systemic therapies, particularly immunosuppressive therapies (such as methotrexate), would form a key aspect of BSC in many patients, despite being used off-label.

The EAG asked their advisers to estimate the extent of use of several BSC therapies in the moderate-to-severe PN NHS population. Table 4 compares these estimates with those reported for the PRIME pooled cohort, both before and during the trial. The comparisons indicate that the use of the following components of BSC, both at baseline and during follow up, are all substantially below what would be expected in an NHS cohort: methotrexate, ciclosporin, systemic corticosteroids, antihistamines, high or super potent TCS and occlusion of TCS. This may seriously limit the applicability of the two PRIME trial results to the NHS setting because, if the PRIME trials had been done in an NHS setting, greater use of these BSC treatments would be expected in participants in the placebo arms than in the dupilumab arms (assuming that the population fits with dupilumab's anticipated license - adults with moderate-to-severe PN who are candidates for systemic therapy); the reliability of the PRIME and PRIME2 efficacy results with respect to the NHS setting are therefore highly uncertain, given these differences in BSC.

The EAG's advisers thought that the use of rescue medication TCS '*as needed throughout the study*' in the PRIME trials, rather than patients being allowed to continue to use pre-trial doses of TCS during the trial, might destabilise disease control in some patients who used high or super potent TCS before the trial. The EAG's advisers also stated that, for patients who do use TCS, many patients would have their lesions occluded, since this may help to maintain the TCS dose and reduce the incidence of lesion scratching (which may lead to improvement in disease severity outcomes such as IGA PN-S). [redacted]

Table 4 Comparison of the BSC used before and during the PRIME trials with the BSC estimated to be used in the NHS

BSC component	*Use in PRIME trials pooled cohort (% of cohort)*			*Estimated use* in moderate-to-severe PN NHS patients (%)*
	Before study entry	*At baseline (randomisation)*	*During 24-week trial period*	
Low-medium potency TCS	Unclear, though 98% had used TCS	Unclear: 59% were on a stable dose of TCS[a] or TCI	NR	>50 (expected to be lower than use of high/super potent as low/medium potency are likely no longer effective for this severity of PN)
High or super potent TCS		0 (prohibited)	[redacted]	>80
Occlusion of TCS	[redacted]	[redacted]	[redacted]	~30 (variable - depends on level of locally available clinical/nursing support i.e. requires patient education)
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

*Estimated by EAG's clinical advisers, [a] Stable regimen defined as maintaining the same medicine (low to medium potency) and frequency of treatment (once or twice daily) used from two weeks prior to screening. [b] Patients with ≥3-month stable dose used prior to randomisation excepted, BSC Best supportive care, CS Corticosteroids, NR Not reported, TCI Topical calcineurin inhibitors, TCS Topical corticosteroids, Sources: Sanofi data on file "Pooled efficacy" (Tables 7, 30-31 & p67)[11]

Summary

In the PRIME trials, the availability of BSC treatments was very limited. Had the PRIME trials been done in an NHS setting, greater use of several BSC treatments would have been expected in the trial placebo arms, than in the dupilumab arms; this would have likely resulted in reduced dupilumab effect estimates (when compared to the PRIME trial results presented in the CS). The PRIME trial populations also had limitations in terms of their applicability to the NHS. The main issue was that around 90% of patients were methotrexate-naïve and that patients were not allowed to take high/super-potent TCS during the screening phase or at randomisation. When taking dupilumab, a 4-point reduction in WI-NRS and achieving an IGA PN-S of 0 or 1 may be more difficult in an NHS population where a significant proportion of patients have had an inadequate response to methotrexate (or lost their response), and where most patients will either be taking high/super-potent TCS at baseline or have had inadequate/lost TCS responses. Given that the mean WI-NRS reduction at 24 weeks was 4.6 (PRIME) and 5.05 (PRIME2), in a more difficult-to-treat population a proportion of patients could drop below the clinically important 4-point threshold.

3.2.2 Results of the PRIME trials

3.2.2.1 Baseline characteristics

The baseline characteristics of participants recruited to the two PRIME trials and the pooled cohort were reported in Table 9 of the CS – reproduced here in an adapted form in Table 5. The EAG's clinical advisers noted that there were a lot more Asian and Hispanic people in the PRIME trials than would be seen in an NHS population. They did not have any strong reasons to believe that PN is different in different ethnic subgroups, however noted a paucity of existing data exploring this. The EAG's advisers also noted that the PRIME populations were around 10 years younger than the population seen in the NHS.

The EAG notes the limited clarity of data provided on the use of TCS. Firstly, TCS use is reported collectively with TCI use (rather than TCS alone). Secondly, it is unclear how many patients had stable low doses versus medium doses. Thirdly, it is unclear how many patients took high/super potent TCS at screening (who then dropped their dose, to become eligible for the trial) as these patients do not fit the definition of 'stable use of TCS/TCI at baseline'. Finally, there are no data on how many patients used methods to occlude their TCS-treated nodules, prior to entering the PRIME trials.

Table 5 Characteristics of participants in the PRIME trials and pooled cohort (adapted from Table 9 of the CS)

Characteristic	PRIME2		PRIME		Pooled ITT analysis	
	BSC (n=82)	Dupilumab (n=78)	BSC (n=76)	Dupilumab (n=75)	BSC (N=158)	Dupilumab (N=153)
Mean Age, years, (SD)	46.7 (15.2)	51.0 (15.8)	51.1 (15.8)	49.2 (17.4)	48.8 (15.6)	50.1 (16.6)
Male (%)	31 (37.8)	26 (33.3)	28 (36.8)	23 (30.7)	59 (37.3)	49 (32.0)
Territory						
North America	14 (17.1)	12 (15.4)	18 (23.7)	17 (22.7)	[redacted]	[redacted]
European Union	37 (45.1)	40 (51.3)	2 (2.6)	1 (1.3)	[redacted]	[redacted]
Rest of World	31 (37.8)	26 (33.3)	56 (73.7)	57 (76.0)	[redacted]	[redacted]
Race, n (%)						
White	48 (58.5)	48 (61.5)	45 (59.2)	35 (46.7)	93 (58.9)	83 (54.2)
Black	5 (6.1)	3 (3.8)	3 (3.9)	8 (10.7)	8 (5.1)	11 (7.2)
Asian	27 (32.9)	25 (32.1)	25 (32.9)	29 (38.7)	52 (32.9)	54 (35.3)
Hispanic or Latino, n (%)	11 (13.4)	10 (12.8)	21 (27.6)	18 (24.0)	32 (20.3)	28 (18.3)
Mean weight (kg) (SD)	75.04 (19.7)	73.86 (17.5)	71.37 (17.0)	75.22 (17.3)	73.29 (18.5)	74.53 (17.3)
Mean BMI, kg/m^2 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PN, years, mean (SD)	5.48 (6.97)	5.36 (6.90)	5.40 (6.21)	6.01 (7.55)	5.44 (6.60)	5.68 (7.21)
History of atopy, n (%)	40 (48.8)	34 (43.6)	28 (36.8)	33 (44.0)	68 (43.0)	67 (43.8)
History of asthma, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stable use of TCS[a]/TCI, n (%)	46 (56.1)	44 (56.4)	45 (59.2)	47 (62.7)	91 (57.6)	91 (59.5)
Mean WI-NRS score (SD)	8.5 (1.0)	8.5 (1.0)	8.3 (1.1)	8.6 (0.9)	8.4 (1.1)	8.6 (0.9)
Mean IGA PN-S score, (SD)	3.4 (0.5)	3.4 (0.5)	3.3 (0.5)	3.3 (0.5)	[redacted]	[redacted]
IGA PN-S categorical score, n (%)						
3 (moderate)	49 (60.5)	49 (62.8)	53 (70.7)	54 (72.0)	102 (65.4)	103 (67.3)
4 (severe)	32 (39.5)	29 (37.2)	22 (29.3)	21 (28.0)	54 (34.6)	50 (32.7)
Mean DLQI score (SD)	18.2 (7.0)	18.2 (6.5)	15.7 (7.3)	17.8 (7.1)	17.0 (7.2)	18.0 (6.7)
Antidepressant use at baseline, n (%)	8 (9.8)	7 (9.0)	9 (11.8)	9 (12.0)	[redacted]	[redacted]

[a] TCS stable regimen defined as maintaining the same medicine (low to medium potency) and frequency of treatment (once or twice daily) used from two weeks prior to screening.

3.2.2.2 Main efficacy results of the PRIME trials

The company reported complete clinical effectiveness results for their primary analysis in Table 12 in CS Section B.2.6.

Table 6 compares the results for the main outcomes of interest using the three different imputation methods for the PRIME and PRIME2 trials individually, and the pooled ITT population. For efficacy

outcomes, treatment with dupilumab resulted in a statistically significant improvement in symptoms of PN for both PRIME and PRIME2. Treatment with dupilumab also significantly increased patient HRQoL- measured as the decrease from baseline in DLQI- in both trials.

Table 6 Summary of results for main outcomes for all imputation methods (adapted from Tables 1-3 in clarification response Appendix 7)

	Primary Method						As-observed Method						Hybrid Method					
	PRIME2		PRIME		Pooled ITT		PRIME2		PRIME		Pooled ITT		PRIME2		PRIME2		Pooled ITT	
	BSC (N=82)	DUPI (N=78)	BSC (N=76)	DUPI (N=75)	BSC (N=158)	DUPI (N=153)	BSC (N=82)	DUPI (N=78)	BSC (N=76)	DUPI (N=75)	BSC (N=158)	DUPI (N=153)	BSC (N=82)	DUPI (N=78)	BSC (N=76)	DUPI (N=75)	BSC (N=158)	DUPI (N=153)
Patients with WI-NRS improvement (reduction) by ≥ 4 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)	[redacted]											
OR (95% CI)	9.0 (3.56, 22.66)		6.5 (2.78, 15.41)		7.6 (4.03, 14.24)		[redacted]											
p-value	< 0.0001		< 0.0001		< 0.0001		[redacted]											
Patients with IGA PN-S 0 or 1 at Week 24																		
Responders, n (%)	13 (15.9)	35 (44.9)	14 (18.4)	36 (48.0)	27 (17.1)	71 (46.4)	[redacted]											
OR (95% CI)	4.4 (2.02, 9.55)		4.0 (1.81, 8.98)		4.2 (2.42, 7.37)		[redacted]											
p-value	< 0.0001		0.0004		< 0.0001		[redacted]											
Patients with both an improvement (reduction) in WI-NRS by ≥4 points and IGA PN-S score of 0 or 1 at Week 24																		
Responders, n (%)	7 (8.5)	25 (32.1)	7 (9.2)	29 (38.7)	14 (8.9)	54 (35.3)	[redacted]											
OR (95% CI)	6.1 (2.03, 18.11)		6.9 (2.49, 19.05)		6.5 (3.05, 13.67)		[redacted]											
p-value	0.0001		< 0.0001		< 0.0001		[redacted]											
Change in DLQI from baseline to Week 24[†]																		
LS, mean (SE)	-6.77 (1.18)	-13.16 (1.21)	-5.77 (1.05)	-11.97 (1.02)	-6.27 (0.77)	-12.56 (0.77)	[redacted]						NR	NR	NR	NR	NR	NR
Difference, (95% CI)	-6.39 (-8.42, -4.36)		-6.19 (-8.34, -4.05)		-6.29 (-7.75, -4.83)		[redacted]							NR		NR		NR
p-value	< 0.0001		< 0.0001		< 0.0001		[redacted]							NR		NR		NR

Abbreviations: BSC: best supportive care; CI: confidence interval; DLQI: dermatology life quality index; DUPI: dupilumab; IGA PN-S: investigator's global assessment 0 or 1 score for Prurigo Nodularis-Stage; ITT: intention-to-treat; LS: least squares; NR: not reported; OR: odds ratio; SE: standard error; WI-NRS = worst-itch numeric rating scale. † Each of the imputed complete data were analysed by fitting an ANCOVA model with the corresponding baseline value, intervention group, documented history of atopy

Table 7 details the proportion of patients who were responders and non-responders with a breakdown of the number of patients who were imputed as non-responders. The breakdown of patients in Table 7 is consistent with the results shown in Table 6; irrespective of the imputation method used the number of responders and non-responders are consistent for all outcomes, therefore all the odds ratios calculated are similar.

There is very little difference in the number of responders and non-responders between the primary and hybrid analyses. While the overall number of responders and non-responders in the as-observed analysis are consistent with the primary analysis, the EAG believes it is important to consider the difference in imputed non-responders to observe the implications of imputation on trial results. In the as-observed analysis patients who received a prohibited or rescue medication were not imputed as non-responders. For the combined WI-NRS improvement of ≥ 4 points from baseline and IGA PN-S 0 or 1 outcome, [redacted] patients in the BSC arm and [redacted] patients in the dupilumab arm had been imputed as non-responders for receiving a prohibited or rescue medication in the primary analysis. Of these patients who received a rescue/prohibited medication, [redacted] in the BSC arm and [redacted] in the dupilumab arm were still imputed as non-responders for either discontinuing the treatment before 24 weeks or for not having an observation for the 24-week time-point. However, of the remaining [redacted] patients in the BSC arm, [redacted] were categorised as non-responders and [redacted] responder. Similarly, in the dupilumab arm, [redacted] additional patients were categorised as non-responders and [redacted] as responders.

The EAG believes that trial conduct could be influential on the impact of any imputation methods used. For the composite outcome of WI-NRS improvement of ≥ 4 points from baseline and IGA PN-S 0 or 1 [redacted] and [redacted] who had been imputed as non-responders due to use of a rescue or prohibited treatment were still considered non-responders when not imputed for. Most patients who were imputed as non-responders received rescue medications, as very few patients in PRIME2 and PRIME received prohibited medications (Table 4). This suggests that rescue treatments had limited efficacy. This could be due to the frequency or method of treatment administration (e.g. whether TCS treatments were occluded). There is also a possibility that patients' condition worsened after randomisation and while patients may have improved enough from their scores taken when they received a rescue/prohibited medication to be considered a responder, when compared to their baseline score they did not qualify as responders. For example, consider a patient with an itch-score of 7 at baseline. By week 6 their itch-score had worsened to 8, at which point they received a rescue treatment after which their itch-score reduced to 4. While their itch-score was reduced by 4 points from the point they received treatment, compared to the baseline score, this reduction would not count as a response as it was only a 3-point reduction. Another possible scenario

is that patients who stopped taking high or super-potent TCS before the trial due to lack of efficacy no longer had any possible rescue medications.

Table 7 Number of responders and non-responders for all imputation methods (adapted from tables in clarification response Appendix 2)

	Primary Analysis		As-observed Analysis		Hybrid	
	BSC (N= 158)	Dupilumab (N=153)	BSC (N= 158)	Dupilumab (N=153)	BSC (N= 158)	Dupilumab (N=153)
Patients with WI-NRS improvement (reduction) by ≥ 4 from baseline to Week 24						
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imputed Non-Responders[†], n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prohibited/Rescue Medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation before week 24, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment period completed, no week 24 data, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with IGA PN-S 0 or 1 at Week 24						
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imputed Non-Responders[†], n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prohibited/Rescue Medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation before week 24, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment period completed, no week 24 data, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weekly average WI-NRS improvement ≥4 points from baseline and IGA PN-S 0 or 1						
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imputed Non-Responders[†], n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prohibited/Rescue Medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation before week 24, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment period completed, no week 24 data, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[†]Two patients, one in the BSC arm and one in the dupilumab arm, were not exposed to the treatment and were imputed as non-responders. **Abbreviations:** BSC: best supportive care

3.2.2.3 Post-intervention follow-up data: from week 24 to week 36

Following the 24-week trial intervention periods there was a 12-week follow-up where patients stopped taking dupilumab or placebo. The company's pooled efficacy report[11] summarised the results by stating that

[redacted]

3.2.2.4 Subgroup analyses

Pre-specified subgroup analyses were presented in Figure 12 (Section B.2.7) of the CS for WI-NRS improvement by ≥4 points from baseline to Week 24. However, the company did not present any results of tests for interaction, to see if there were any statistically significantly subgroup differences. The EAG found these results in the CSRs and pooled efficacy reports.

[redacted]

[redacted]

3.2.2.5 Adverse events

Adverse events (AEs) were presented in Section B.2.10 of the CS. The company reported safety results from primary cut-off dates for both PRIME2 (12th November 2021) and PRIME (30th August 2021). All safety analyses were performed on the safety population and were descriptive.

Treatment-emergent adverse events

In the pooled safety analysis, 97 (63.8%) patients in the dupilumab group and 89 (56.7%) patients in the BSC group experienced at least one treatment-emergent adverse event (TEAE).

A brief summary of TEAEs is given in Table 8. [redacted] More patients in the dupilumab arm experienced at least one TEAE (n = 97; 63.8% in the pooled analysis) compared to the BSC treatment arm (n=89; 56.7%), but fewer patients in the dupilumab arm experienced at least one severe TEAE (n=5; 3.3% compared to n=9; 5.7% in the BSC arm) or treatment-emergent SAE (n=7; 4.6% compared to n=12; 7.6%).

Table 8 Summary of treatment-emergent adverse events in PRIME2, PRIME and the pooled safety analysis (Adapted from CS Table 13 and the CSRs for PRIME2 and PRIME)

	PRIME2		**PRIME**		**Pooled Analysis**	
n (%)	BSC (N= 82)	DUPI (N=77)	BSC (N=75)	DUPI (N=75)	BSC (N=157)	DUPI (N=152)
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	89 (56.7)	97 (63.8)
Severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]	9 (5.7)	5 (3.3)
Treatment-emergent SAE	[redacted]	[redacted]	[redacted]	[redacted]	12 (7.6)	7 (4.6)
TEAE leading to death	[redacted]	[redacted]	[redacted]	[redacted]	0	0

TEAE leading to permanent treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	4 (2.5)	0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; AESI: adverse event of special interest; BSC: best supportive care; DUPI: dupilumab; IMP: investigational medicinal product; SAE: severe adverse event; TEAE: treatment-emergent adverse event

A summary of TEAEs observed in the pooled safety population is presented in Table 14 in Section B.2.10.2 of the company submission. The most commonly reported TEAEs (≥ 10%) in the pooled safety population were [redacted]

TEAEs that were reported more frequently in the dupilumab arm compared to the BSC arm with a difference of at least 1% in the pooled analysis were: nasopharyngitis ([redacted]); dizziness ([redacted]), diarrhoea ([redacted]), eczema ([redacted]), an increase in blood creatine phosphokinase levels ([redacted]), conjunctivitis ([redacted]), allergic conjunctivitis ([redacted]), myalgia ([redacted]), and accidental overdose ([redacted]).

[redacted]

[redacted]

AESIs and other selected AEs

AESIs are summarised in Table 15 in the CS Section 2.10.3.

[redacted]

Dupilumab-associated ocular surface disease

The MHRA has issued a warning for dupilumab regarding the risk of ocular adverse reactions.[12] This warning is a result of an increase in the incidence of ocular complications in patients treated with dupilumab, which are collectively known as dupilumab-associated ocular surface disease (DAOSD).[13, 14]

DAOSD is more prevalent in patients receiving dupilumab for the treatment of AD compared to patients being treated for asthma or CRSwNP.[13] The prevalence of DAOSD in patients that are receiving dupilumab for PN is unknown, but our clinical advisers agreed with the company's advisory board who believed that the prevalence of DAOSD in patients with PN would be lower than in AD.[4]

[redacted] A summary of the ocular AEs observed in in the pooled population of PRIME and PRIME2 is presented in Table 9.

[redacted]

Table 9 Summary of ocular AESIs in the pooled safety population

n (%)	**BSC (N=157)**	**Dupilumab (N=152)**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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

[a]Labeling subgroup of preferred terms included in the USPI for dupilumab.

Abbreviations: AESI: adverse event of special interest; BSC: best supportive care, FDA: Food and Drug Administration; USPI: United States prescribing information. Source: Adapted from Table 19 of the pooled safety report[15]

EAG Comments

DAOSD is an AE of special interest and the MHRA's guidance on the management of people with DAOSD will be an important resource; however, the EAG believes that this will not have implications on the cost-effectiveness models for dupilumab.

While it is still unclear what proportion of patients with PN will be affected by DAOSD in clinical practice, the EAG's and company's clinical advisers agree that it is likely not to be as common as it is in AD. The clinical advisers were also in consensus that they are sufficiently familiar with DAOSD in a dermatological setting that for most mild-moderate cases they would be able to manage patients within dermatology services without having to refer them for specialist ophthalmological care. Therefore, the EAG believes that any costs incurred in the management of patients with DAOSD would be minimal.

In their response to clarification question A12, the company provided a summary of AEs observed in dupilumab trials for all indications.

[redacted]. The safety results observed in the PRIME2 and PRIME trials are consistent with the safety profile observed in other indications. It is unclear why ocular AEs are more common in some indications only.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company conducted an SLR to identify relevant studies (Section 3.1). However, most of the studies identified were non-RCTs (n=21) for immunosuppressants, antidepressants, antiepileptics, and antihistamines and were deemed low quality by the company. The seven RCTs that were identified involved treatment with antibody therapies, opioids, neurokinin 1 antagonists, and topical therapies.

The company also commissioned a feasibility assessment for an indirect treatment comparison (ITC) to compare the clinical efficacy of dupilumab relative to relevant comparators.[16] The SLR for the feasibility report identified 7 RCTs and 20 non-RCTs. The studies identified by this SLR were consistent with those identified in the SLR in CS Appendix D. The one study missed in the feasibility assessment SLR was published after the search was conducted.[17] In this feasibility assessment, the company identified only nemolizumab, nalbuphine, ciclosporin and methotrexate as comparators of interest. The feasibility assessment did not identify any common endpoints between PRIME and PRIME2 and studies for methotrexate and ciclosporin, therefore an ITC was deemed not to be feasible. According to the feasibility assessment, an ITC could be conducted to compare patients in the dupilumab trial who did not receive TCS/TCIs and either nemolizumab or nalbuphine. However, neither of these drugs were considered relevant comparators according to the NICE scope.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company did not conduct an indirect treatment comparison. In the CS (Section B.2.9), the company stated that this was due to the absence of any licensed or NICE-recommended targeted systematic therapies for PN, as well as a lack of RCT evidence on off-label treatments.

The EAG agrees with the company's reasons for not conducting an ITC. Most studies for the comparators identified in the SLR are generally small, non-randomised, and differ in terms of baseline characteristics and trial conduct; estimates from such an ITC are likely to not be robust, and at risk of bias.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Studies not included in the company's SLR

The CS stated that the only identified studies investigating ciclosporin and methotrexate were non-RCTs with ≤14 patients. The EAG identified two larger studies which seemed relevant to the appraisal; one does not appear to have been identified by the company (Klejtman et al. 2018)[7] and the other (Grundel et al. 2020)[6] was excluded because there was "No intervention". The EAG found results relating to interventions in the Grundel et al. 2020 study and summarises the methods, characteristics, and results from both studies in **Error! Reference source not found.**.

Table 10 Details of studies of methotrexate or ciclosporin which were not included in the company's systematic review

	Study	
	Grundel et al. 2020	Klejtman et al. 2018
N	325 (74 took methotrexate or ciclosporin)	39
Design & setting	Retrospective Germany	Retrospective France
Population	'Chronic nodular prurigo' (not defined). Baseline data not presented for the immunosuppressant subgroup (n=74)	Prurigo rather than prurigo nodularis specifically. Median PNRS 4 Median lesion extent: 2 ('Moderate') Patients had previous failure of topical steroids, H1-antihistamine drugs or phototherapy
Age (median)	62 years (for N=325)	62 years
Intervention	Immunosuppressants (methotrexate or ciclosporin, N=74)	Methotrexate median weekly dose: 15 mg
Outcomes	Dynamic Pruritus Score, % change from treatment initiation: <30% non-responders (NR), 30-49% weak responders (WR), 56-69% good responders (GR), ≥70% very good responders (VGR)	Pruritus improvement rated as: not (NI), moderately (MI) or very much (VMI). Dermatologist assessment of lesions: Complete response (CR, complete healing), partial response (PR, significant but incomplete improvement), failure (F, no improvement or worsening)
Results	6 NR (8%), 2 WR (3%), 10 GR (14%), 56 VGR (76%)	At 6 months, pruritus: 72% VMI, 19% MI, 9% NI At 6 months, lesions assessment: 56% CR, 38% PR, 6% F. 3 and 12 month data also reported. 4 patients stopped treatment because of AEs
Limitations	Retrospective recruitment. Baseline data limited and not available for N=74 subgroup. No outcomes on nodular lesion status. Treatment duration determined by the time between the first consultation and the follow-up timepoint with the highest response category (median duration for GR 169 days, VGR 182 days). Results focus on larger cohort (most of which took other treatments).	Retrospective recruitment. Very basic outcome/assessment measures. Small sample size. Population is prurigo rather than prurigo nodularis specifically.

AEs Adverse events, PNRS Pruritus numeric rating scale

Both studies are quite small and have important methodological limitations and uncertainties. Nevertheless, they do indicate that methotrexate and ciclosporin may be effective treatments for PN for improving pruritus (assessed in both studies) and nodule healing (assessed in Klejtman et al. 2018). Given the estimated prevalence of use of these treatments (and other systemic treatments, see Table 4) in the NHS PN population, the results from these studies suggest that their prohibition in both PRIME trials limits the applicability of the trial results to the NHS setting.

3.6 Conclusions of the clinical effectiveness section

The evidence presented in the CS on the efficacy and safety of dupilumab was based on the results of the randomised PRIME and PRIME2 trials. Although these studies showed that dupilumab produces statistically significant improvements in clinically relevant outcomes, their results have limited applicability to the NHS setting, when considering the comparators and populations studied.

In the PRIME trials, the availability and use of BSC treatments was very limited because many treatments were prohibited during the trials. Had the PRIME trials been done in an NHS setting, greater use of several BSC treatments would have been expected in the trial placebo arms, than in the dupilumab arms. This would have likely resulted in reduced dupilumab effect estimates (when compared to the PRIME trial results presented in the CS).

The PRIME trial cohorts were comprised of largely methotrexate-naive participants; these may be easier to treat (i.e. more likely to achieve responses to the key trial outcomes) than the more methotrexate-experienced population likely to be treated with dupilumab in the NHS. Also, in both PRIME trials, participants on stable regimens of high potency or super potent TCS at screening were required to decrease to medium potency TCS to become eligible for trial inclusion. The magnitude of the responses in these patients may be greater than would have been seen had the trials allowed the continuation of stable regimens of high/super potent TCS (as the disease may have been a little better controlled in these patients).

[redacted]

The lack of RCT evidence for comparator therapies meant the company could not conduct any indirect treatment comparisons. However, the company's systematic review did not include two studies which were useful for indicating how effective methotrexate and ciclosporin might be.

Dupilumab appears to have an acceptable and largely manageable safety profile.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company's systematic literature review did not identify any economic evaluations for the treatment of adults with PN. See Appendix G of the CS for a detailed description of the searches and results of the review. One published cost-effectiveness study of chronic pruritus was identified from an additional targeted literature review for pruritus, but the simple model structure used in this study was not considered reflective of the treatment pathway, disease natural history and outcomes for PN. The company also summarised three previous cost-effectiveness models used in NICE Technology Appraisals to evaluate treatments for moderate to severe AD: TA534 (dupilumab), TA681 (baricitinib) and TA814 (abrocitinib, tralokinumab or upadacitinib) because PN and AD share similarities as type 2 inflammatory skin diseases.

Points for critique

The literature searching for the company's review of cost-effectiveness evidence appears to have been conducted to a high standard and is well reported – See Appendix 1 for details. The EAG considers that all relevant publications are likely to have been identified.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The company submitted a *de-novo* model to compare the cost-effectiveness of dupilumab, as an adjunct to best supportive care (BSC) compared to BSC alone. A decision tree structure is used to assess patients' response to treatment with dupilumab plus BSC, or BSC alone, and a Markov model to estimate long-term health outcomes and costs conditional on response to treatment. In the decision tree, patients, for both comparators, are assessed for treatment response at 24 weeks and classified as either responders or non-responders. Following assessment of response, patients classified as responders to dupilumab plus BSC remain on treatment until they discontinue treatment due to loss of response, adverse events, patient or clinician preference, at which point they receive BSC only. Patients classified as non-responders to dupilumab plus BSC at week 24, discontinue treatment with dupilumab and receive BSC only. Patients assessed for response to treatment with BSC at week 24 continue to receive BSC over time, irrespective of their response status, but the model tracks responders and non-responders to BSC because disease management costs and health-related quality of life utility values differ by response status. All patients are at a risk of all-cause mortality, which is not affected by PN.

Dupilumab is modelled to affect quality-adjusted life years (QALYs) by increasing the proportion of patients who respond to treatment, which is associated with improved health-related quality of life

compared to BSC. Non-responders to dupilumab are also modelled to have better quality of life than BSC, despite moving to treatment with BSC only. The addition of dupilumab to BSC increases NHS costs due to its acquisition cost, with some of this cost offset by lower disease management and rescue medication costs associated with better treatment response compared to BSC.

4.2.1 NICE reference case checklist

The model submitted by the company is assessed in relation to the NICE reference case in Table 11.

Table 11 NICE reference case checklist

Element of health technology assessment	**Reference case**	**EAG comment on company's submission**
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate.
Perspective on costs	NHS and PSS	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate. The time horizon is lifetime of 50 years.
Synthesis of evidence on health effects	Based on systematic review	The CS is appropriate. The systematic review identified two clinical trials for dupilumab in the relevant patient population: PRIME2 and PRIME.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life (HRQoL) in adults.	The CS is appropriate. HROoL was measured with EQ-5D-5L and valued using the UK tariff. The EQ-5D-5L was converted to EQ-5D-3L using appropriate algorithms by Hernández Alava[18] (base case) and van Hout[19] (sensitivity analysis)
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate.

Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.
CS: company submission; PSS: personal social services; QALYs: quality-adjusted life years; EQ-5D: standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

4.2.2.1 Summary of company submission

The model is a cohort model, with a decision tree and Markov model (see Figure 1 and Figure 2Error! Reference source not found. for the decision tree and Markov components, respectively). The model starts with a 24-week decision tree to reflect the intervention period of 24 weeks used in the PRIME2 and PRIME trials. Patients enter the decision tree at the beginning of treatment on either dupilumab plus BSC or BSC alone. At 24-weeks, patients are assessed for response to treatment according to the efficacy response criteria (see Section 4.2.6.1), where patients on dupilumab plus BSC are classified as either (i) dupilumab plus BSC responders or (ii) dupilumab plus BSC non-responders, and patients on BSC alone are classified as either (i) BSC responders or (ii) BSC non-responders. At 24-weeks, patients exit the decision tree and enter the Markov model with a lifetime horizon until death. The cycle length used in the model is 12 weeks, and a half-cycle correction is implemented.

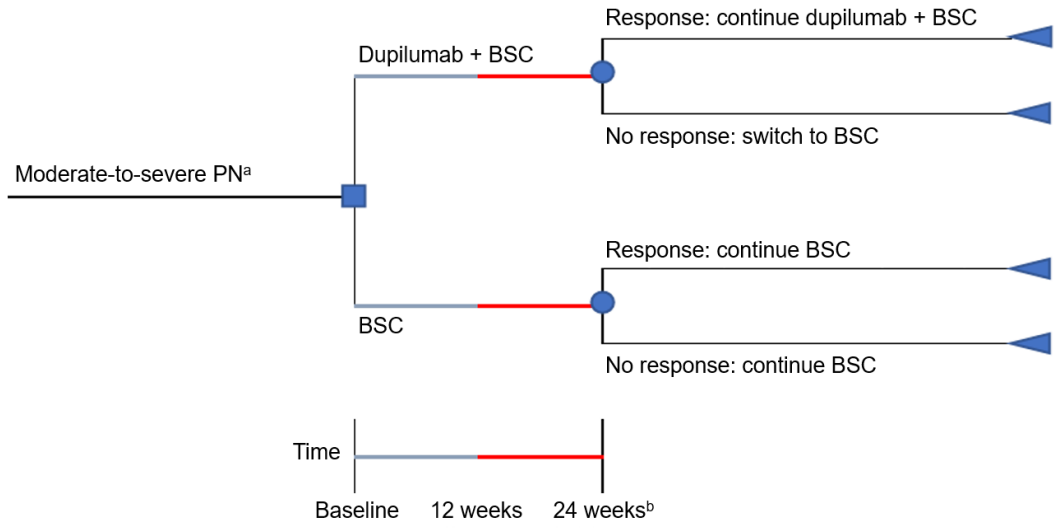
The treatment response states included in the Markov model are:

- 'Response', which represents the time when patients who achieve response at 24-weeks persist on treatment until discontinuation due to loss of response, adverse events or patient/clinician preference. During maintenance treatment, health-related quality of life improvements for responders compared to non-responders at week 24 are maintained for patients responding to treatment over time and are treatment-specific. The rate of discontinuation is also treatment-specific.
- 'No Response', which represents all non-responders to treatment. This includes patients who do not achieve response to treatment at week 24 and patients who lose response over time by moving from the 'Response' to the 'No response' state, despite achieving an initial response at 24-weeks. All patients in the 'No response' state receive BSC treatment; however, health-related quality of life for non-responders is treatment-specific.

All patients are at an equal risk of all-cause mortality, which is not affected by PN.

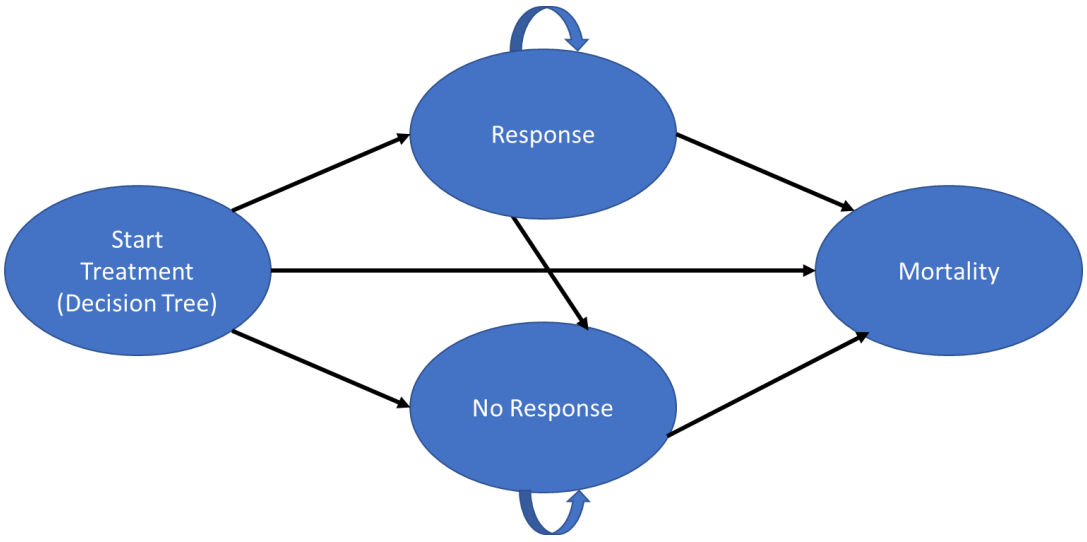
The CS acknowledges that there is a chance that some patients could move from the 'No Response' to the 'Response' state for a short period of time due to symptomatic improvement on systemic therapies, but this transition is not modelled.

Figure 1 Cost-effectiveness model structure (reproduced from CS Figure 14, page 67)



Abbreviations: BSC: best supportive care; PN: prurigo nodularis.
[a]Moderate to severe PN is defined as prurigo nodularis inadequately controlled with topical prescription therapies or when these therapies are not appropriate.
[b]The clinical assessment timepoint in the PRIME2 and PRIME trials was 24 weeks.

Figure 2 Markov model structure using treatment response states (reproduced from CS Figure 15, page 68)



Points for critique

The EAG considers the model structure to be broadly representative of the natural course of PN, where treatment is expected to provide a symptomatic improvement in health-related quality of life and control of symptoms, but not extend length of life. The model structure is similar to that seen in

previous NICE Technology Appraisals for AD, including dupilumab for moderate to severe AD (TA534). However, the EAG notes a couple of structural assumptions that are not adequately justified in the CS.

First, when patients exit the decision tree at 24 weeks and enter the Markov model based on response to treatment, BSC responders are separated from BSC non-responders, yet patients treated with BSC remain on the same treatment regardless of their response status. The company justified this approach on the basis that health-related quality of life utility values and costs in BSC differ by response status, and acknowledged concerns raised about the model structure used for AD during the appraisal of TA534, where the model split 'responders' and 'non-responders' into different states for dupilumab, but did not for BSC. In line with the amended AD model in TA534, patients on BSC are modelled separately in order to reflect the differences in utility achieved by those who respond to treatment and those who do not. The EAG agrees that differences in health-related quality of life utility values and costs by treatment response should be reflected in the model for BSC but notes that a *weighted* average of utility values and costs for responders and non-responders to BSC at week 24 could be used to represent those treated with BSC in the model, without explicitly creating separate treatment states for responders and non-responders to BSC (note that the appraisal committee's primary concern in TA534 was that an average utility value from everyone having BSC was used for all non-responders in the original AD model). The creation of separate treatment states for BSC responders and BSC non-responders in the model means that an additional assumption about long-term discontinuation on BSC is required to model the transition from the 'Response' to 'No response' state, even though patients are not discontinuing BSC treatment. The fact that some patients may respond better to BSC treatment than other patients over time may still be modelled by appropriately weighting the utility values and costs in a BSC treatment state.

A weighted BSC treatment state by likelihood of response to BSC may also be more appropriate for estimating the utility values and costs associated with dupilumab plus BSC non-responders, who are assumed to discontinue active treatment and continue on BSC only. For these patients, the model applies separate utility values for dupilumab plus BSC non-responders from BSC non-responders, while costs for disease management and rescue therapy medications are assumed to be the same for all non-responders regardless of initial treatment. This creates inconsistencies in the way that non-responders are modelled over time. The fact that treatment with BSC is defined the same under both treatment options (i.e., dupilumab plus BSC and BSC alone) it would seem reasonable to assume that non-responders who continue on BSC only would be expected to have the same utility values and costs associated with BSC.

item 1. A BSC treatment state, with utility values and costs weighted by the likelihood of response to BSC over time, is likely to better reflect fluctuations in response to standard

treatment without dupilumab over time (e.g., from the use of systemic therapies). Ideally the model would discount any placebo effect from the results of the trials and then just model the true effect of BSC as the background treatment for all patients, including dupilumab non-responders.

Second, the use of a treatment-specific discontinuation rate from the 'Response' to 'No response' state for responders to treatment with dupilumab plus BSC and BSC alone (who remain on BSC) creates a large difference in the percentage of responders to treatment over time compared to that observed at week 24 in the clinical trials. This has implications for the utility values and costs included in the model by increasing the difference between dupilumab plus BSC and BSC alone during the extrapolation phase compared to that observed in the first 24 weeks (see Section 4.2.6.2 below for further details).

item 2. A discontinuation rate for BSC responders is not required in the model because these patients remain on BSC treatment.

4.2.3 Population

4.2.3.1 Summary of company submission

The patient population in the model is adults with moderate-to-severe PN who have had inadequate response or intolerance to existing topical prescription therapies, which is expected to represent the licenced indication for dupilumab in PN. The definition of inadequately controlled matches the eligibility criteria for the PRIME2 and PRIME trials (i.e., patients unable to achieve and/or maintain remission and low disease activity despite treatment with a daily regimen of medium-to-super potent TCS applied for at least 14 days or the maximum duration recommended by the product prescribing information, whichever is shorter).

The baseline characteristics are based on the average patient population in the pooled PRIME2 and PRIME trials, which is 49.5 years of age, with 34.7% male, weight 73.9 kg and average duration of PN of 5.56 years (see Table 9, p33 of CS).

No separate subgroup populations are considered in the company's base case analysis.

Points for critique

As discussed in Section 3.2.1.1, the EAG has concerns about how well the patient population of the PRIME2 and PRIME trials align with the PN population seen in UK clinical practice. This has an impact on the baseline population characteristics used in the model and the average baseline EQ-5D utility value ([redacted]) and WI-NRS (8.493) and DLQI (17.49) scores.

To understand the prevalence of PN in the UK, the company conducted a study that utilised the CPRD Aurum and Gold databases linked to data from Hospital Episode Statistics (HES) for patient records between 2007 and 2019.[20] This study identified 8,933 patients with PN in England, of which 2,498 patients (28%) required systemic treatment and were therefore classified as having moderate-to-severe PN. The average patient demographics reported in this study were 61 years of age and 43% male, which suggests that the population seen in the UK may be older on average than those included in the PRIME2 and PRIME trials. Differences may also be expected in the average WI-NRS and DLQI scores and baseline EQ-5D.

item 3. Baseline population characteristics of age, weight, percentage of male, duration of PN, WI-NRS score, DLQI score and EQ-5D utility value in the PRIME trials may not match those seen in UK clinical practice.

4.2.4 Interventions and comparators

4.2.4.1 Summary of company's submission

The intervention and comparator in the model are dupilumab plus BSC and BSC alone, respectively. BSC is defined based on the treatment regimens used in the placebo arm of the PRIME2 and PRIME trials, which was a combination of emollients and low-to-medium potency TCS/TCI. Rescue therapy of high potency or super potent TCS/TCI was also available to all patients in the trials. BSC is the same for both dupilumab plus BSC and BSC alone.

BSC used in the model includes mild/moderate TCS, TCI and rescue therapy. The CS assumes that patients will use 100g of TCS every 2 weeks, and 100g of TCI every 6 weeks based on the British National Formulary, which indicates that a once daily application of TCI will last for 2 weeks of treatment for application of 100g to trunk or legs and 30-60g to arms, while application of tacrolimus for moderate-to-severe atopic eczema (which the company assumes for the duration of TCI) is twice weekly with 0.1% of ointment to be applied thinly, with an interval of 2-3 days between applications. Therefore, instead of requiring 14 days for 100g of TCI, application is assumed to be one-third less frequent than TCS in the model. Rescue therapy includes super potent TCS/TCIs as used in the trials, which is assumed to have a duration of 14 days. The dosage, usage and frequency for BSC medications, including rescue therapy, are presented in the CS in Tables 39 (p98) to Table 42 (p99).

The cost-effectiveness of dupilumab plus BSC is assessed using the same dose of dupilumab as that used in the PRIME2 and PRIME trials, i.e., an initial dose of 600 mg (two 300 mg administered in different injection sites), followed by 300 mg given every two weeks by subcutaneous injection until discontinuation or death.

Points for critique

As discussed in Section 2.3 and Section 3.2.1, the EAG has a number of concerns about the how well the treatment regimens used in the placebo arm of the pooled PRIME trials matches with what constitutes BSC in UK clinical practice. The BSC therapies used in the trials are much more conservative than those commonly used in NHS practice, where BSC in the NHS is likely to include one or more of: a high- or super-potent TCS, a systemic immunosuppressant, most commonly methotrexate or ciclosporin, an antidepressant, antihistamines, and oral steroids. In the trials, systemic immunosuppressants, antihistamines and oral steroids were prohibited medications. High- or super-potent TCS were only allowed as rescue therapy and antidepressants only permitted in participants who were taking stable doses before randomisation. Furthermore, [redacted] and only [redacted] of the PRIME cohort had previously used methotrexate, which is a key treatment used in the NHS. As a consequence, the EAG believes that the populations in the trials may represent an easier to treat population (i.e., more likely to achieve response to the key trial outcomes).

The company have adopted a pragmatic approach to modelling where no consideration has been given to the sequence of treatments (or step-up or step-down of constitutes of BSC based on response to therapy), which the EAG considers to be reasonable because there is no standardised approach to treatment sequencing in UK clinical practice.

> ***item 4. The treatment regimens used in the placebo arm of the pooled PRIME trials are unlikely to match that used for BSC in UK clinical practice.***

4.2.5 Perspective, time horizon and discounting

4.2.5.1 Summary of company's submission

The analysis is conducted from the perspective of the NHS and Personal Social Services (PSS) over a 50-year lifetime horizon, at which point the model predicts that nearly all patients in the cohort have died. A 3.5% annual discount rate is used for both costs and health effects. Scenario analysis is conducted on the inclusion of costs related to lost productivity.

Points for critique

The CS adheres to the NICE health technology evaluations manual[21] and the EAG considers the approach used by the company to be appropriate. Lost productivity costs are excluded from the company's base case results and only included in a scenario analysis.

4.2.6 Treatment effectiveness and extrapolation

The model includes three elements relating to treatment effectiveness and extrapolation of effects over the long-term, which are discussed below in turn: (i) response criteria; (ii) long-term treatment effect; and (iii) mortality.

4.2.6.1 Response criteria

The efficacy response criteria are used to define which patients are responders to treatment at week 24 and continue on treatment, or discontinue treatment and move to the 'No response' state in the model. In the PRIME2 and PRIME trials, response to treatment, as assessed by the primary endpoints, was defined by improvement in WI-NRS (i.e., a reduction ⩾4 from baseline to Week 24). However, the response criterion used in the model is the composite of WI-NRS improvement ⩾4 and IGA-PN-S reduction ⩾1 from baseline, in the base case analysis, while WI-NRS improvement ⩾4 is used in a sensitivity analysis. The company states that the combined response criterion was supported by UK clinicians in an advisory board conducted in December 2022.

Based on the response criterion, the model is populated with data that represent the probability of achieving the selected response criteria for each model comparator. Response data from the studies is further delineated using the 'as observed with multiple imputation' (as observed + MI) method, where patients requiring rescue therapies who met the designated response criteria were still counted as responders in the pooled data from the PRIME2 and PRIME trials; however, these patients were censored in the primary endpoint analysis of the trials. Table 12 summarises the probability of response at week 24 used in the decision tree model for the base case analysis and for alternative response criteria.

Table 12 Summary of week 24 response rates

Response criteria	Dupilumab plus BSC, %	BSC, %	Difference between treatments, %
WI-NRS improvement ≥ 4 and IGA-PN-S reduction ≥ 1 from baseline to week 24 (base case analysis)			
As-observed + MI* **(represents base case)**	[redacted]	[redacted]	[redacted]
Primary endpoint analysis†	[redacted]	[redacted]	[redacted]
WI-NRS improvement ≥ 4 from baseline to week 24 (sensitivity analysis)			
As-observed + MI*	[redacted]	[redacted]	[redacted]
Primary endpoint analysis†	[redacted]	[redacted]	[redacted]

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.
* Includes patients requiring rescue therapies who met response criteria.
†Excludes patients requiring rescue therapies (censored from the primary endpoint analysis of the trials).

Points for critique

The EAG has two main concerns with the efficacy evidence informing the cost-effectiveness model. The first is the limited justification for using the composite response criterion of WI-NRS improvement ⩾4 and IGA-PN-S reduction ⩾1 from baseline in the base case analysis. Although the EAG considers it appropriate to include both a measure of the intensity of itch and nodular lesion severity score, the EAG is less clear why the response criterion of IGA-PN-S reduction ⩾1 was not considered a key primary or secondary outcome measure in the PRIME2 and PRIME trials but is considered important for the economic modelling. A key secondary endpoint in the PRIME trials was the proportion of participants with IGA PN-S 0 or 1 score at week 24, while another key secondary endpoint in the trials was the proportion of participants with both an improvement (reduction) in WI-NRS by ≥4 from baseline to week 24 and an IGA PN-S 0 or 1 score at week 24. For consistency with the endpoints used in the trial, the EAG considers it more appropriate to use IGA PN-S 0 or 1 score in the composite response criterion used in the model, rather than IGA-PN-S reduction ⩾1; the former was considered a key outcome in the trials and represents a clear improvement in disease severity, while the latter may be less discriminatory in disease severity score (for example, a change in abundant lesions of 105 to 95 would represent a move from IGA PN-S score of grade 4 to grade 3 but this change is less likely to have significant impact on symptom control and health-related quality of life compared to a change to IGA PN-S score of grade 0 or 1).

At points for clarification the EAG requested the response rates for the composite response criterion of WI-NRS improvement ⩾4 from baseline and IGA-PN-S score of 0 or 1 at week 24 using the as observed + MI method and pooled ITT analysis (Table 13). The EAG considers Scenario 1 in Section 6.1.1.1 that assesses the cost-effectiveness of dupilumab plus BSC relative to BSC alone using the response rates for the composite response criterion of WI-NRS improvement ⩾4 from baseline and IGA-PN-S score of 0 or 1 at week 24.

Table 13 Week 24 response rates for WI-NRS improvement ⩾4 and IGA-PN-S score of 0 or 1.

Response criteria	Dupilumab plus BSC, %	BSC, %	Difference between treatments, %
WI-NRS improvement ⩾ 4 and IGA-PN-S score of 0 or 1 from baseline to week 24 (EAG scenario)			
As-observed + MI*	[redacted]	[redacted]	[redacted]
Primary endpoint analysis†	[redacted]	[redacted]	[redacted]

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.
* Includes patients requiring rescue therapies who met response criteria.
†Excludes patients requiring rescue therapies (censored from the primary endpoint analysis of the trials).

item 5. The EAG considers that the combined response criterion of WI-NRS improvement ⩾4 from baseline and IGA-PN-S score of 0 or 1 at week 24 may be more relevant for

assessing treatment response than the combined criterion of WI-NRS improvement ⩾4 and IGA-PN-S reduction ⩾1 because the former is consistent with the key endpoints used in the PRIME trials.

The second concern relates to the appropriateness of not considering a measure of improvement in quality of life (such as the patient reported DLQI) in the response criterion. As noted in the CS, PN shares many similarities with the analogous disease area of AD, where the signs and symptoms of both manifest with an impact on health-related quality of life and disease burden. In AD, an adequate response to dupilumab is based on:[5]

- at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50), and
- at least a 4-point reduction in the DLQI from when treatment started.

The appraisal committee for TA534 understood that disease severity for AD was based on both clinical signs and on patient-reported symptoms and concluded that NHS clinicians routinely use the dermatology-specific DLQI to assess quality of life in skin conditions. It is worth noting that the primary endpoints of the clinical trials for dupilumab in AD (SOLO 1 and 2, CHRONOS and CAFÉ) included either EASI 75 or the combined EASI 75 and IGA score of 0 or 1 and ≥2-point improvement from baseline, while DLQI was included only as a secondary endpoint in the same way as it is included in the PRIME2 and PRIME trials for PN. The EAG considers there to be variability in the way response to treatment is assessed in PN and, as indicated in the CS, WI-NRS and IGA-PN-S are not routinely used to assess response in current UK clinical practice. Therefore, the EAG believes consideration should be given to an improvement in the DLQI score for the assessment of response to PN treatment.

item 6. The EAG considers an improvement in the DLQI to be important when considering adequate response to dupilumab in PN.

4.2.6.2 Long-term treatment effect and response waning

The model is designed to estimate the long-term benefit of treatment beyond the extent of the observed trial evidence; however, there are no extension studies to allow for estimation of the long-term effectiveness of dupilumab or BSC in PN. The company assumes that patients who achieve response at 24-weeks persist on treatment until discontinuation due to loss of response, adverse events or patient/clinician preference. During maintenance treatment, health-related quality of life improvements for responders at week 24 are maintained for patients responding to treatment over time until treatment discontinuation. The model includes an annual rate of treatment discontinuation for responders to dupilumab plus BSC and BSC alone (although BSC patients do not discontinue treatment). In addition to the annual rate of discontinuation, the model also includes assumptions

regarding response waning over time, for both comparators, to reflect the loss of treatment response for patients with PN after exiting the controlled clinical trial environment.

Annual discontinuation rates

The annual discontinuation rate is implemented as a transition probability from the 'Response' to 'No response' treatment states in the Markov model. In the base case analysis, the model uses pooled all-cause treatment discontinuation rates from the PRIME2 and PRIME trials as a proxy for the loss of response over the modelled time horizon. Therefore, the model assumes differential annual discontinuation rates for dupilumab plus BSC ([redacted]) and BSC alone ([redacted]). Although BSC patients do not discontinue treatment, the movement from the 'Response' to 'No response' for these patients is included in the company's model to account for the accrual of different utilities and costs for BSC over time. The annual discontinuation rate for dupilumab plus BSC taken from the PRIME2 and PRIME trials is similar to the rate used in the appraisal of dupilumab in AD ([redacted]; TA534).

Response waning

The company noted that in the pooled analysis of the PRIME2 and PRIME trials, there was a high treatment response rate in both the BSC and dupilumab plus BSC arms, a similar effect to that observed in the clinical trials for AD. Therefore, the company applied response waning assumptions to all treatments to represent a loss of response over time, based on methodology used in the AD appraisals (TA534, TA681 and in the multiple technology appraisal for upadacitinib, abrocitinib and tralokinumab), which are predicated on (CS, p73):

- Improved adherence to treatment due to regular clinic visits as part of the trial programme;
- Increased access to healthcare facilities and professionals as part of the trial programme;
- Access to best and continuously optimised BSC, including timely rescue treatments.

The company argues that it is improbable that the observed effect size for BSC alone would persist once patients have completed the trials and are outside the protocol-driven clinical trial setting where behaviours, particularly around the adherence to topical treatments, are mandated. Also, in routine clinical practice, patients are likely to either stop or switch to other treatments if their current treatment is no longer effective or associated with adverse effects. The concept of loss of treatment response was incorporated in the model to account for removal of the protocol driven trial effect from week 24 onwards.

Because there are no extension studies to allow for estimation of the real-world effectiveness of dupilumab or BSC in PN, the probability of sustained response (and maintenance of health-related quality of life) over time was informed by evidence relating to the use of dupilumab for the treatment of AD and from qualitative interviews with clinicians and a structured expert elicitation (SEE)

exercise. The SEE exercise was undertaken to elicit how health-related quality of life might be maintained at three distinct time points (6 months, 1 year and ≥2 years) for patients with PN, after they leave the protocol-driven environment of the PRIME2 and PRIME trials and return to real-world clinical practice. The results of the SEE exercise are only used in the base case analysis to inform the proportion of utility maintained at each of the three time points for non-responders to treatment (see Section 4.2.8.4 for details on the SEE). The following text summarises the justification and chosen data inputs used in the CS for treatment response waning.

Maintenance of treatment effect in dupilumab plus BSC patients

The company states that clinicians in the UK, who have experience of the use of dupilumab for the treatment of AD, expect benefits associated with dupilumab response in PN to be maintained in a post-trial setting for patients who continue to receive treatment. In the absence of long-term data for dupilumab in PN, the CS uses data from the dupilumab in AD open-label extension study, which demonstrates that use of dupilumab over the longer term is associated with maintained or increased benefit in AD.[22] In the base case analysis, the probability of dupilumab plus BSC patients having a sustained response in year 2 is 91.4%, while the corresponding values in years 3, 4 and 5+ are 97.2%, 90.9% and 90.9%, respectively (see Table 23 of CS, p80). For a sensitivity analysis, the company used the NICE-accepted data from TA534 in AD, which translated into within-year conditional proportion of remaining patients with maintenance of benefit of 98%, 96.9%, 97.9% and 98.9% in year 2, 3, 4 and 5+, respectively.

Maintenance of treatment effect in BSC patients

The company states that the treatment effect in BSC alone from the PRIME2 and PRIME trials would not be maintained outside the protocol-driven clinical trial setting. To inform the maintenance of response on BSC from week 24 onwards, the company assumed that 25% of the benefit would be lost in year 2, 50% in year 3, 75% in year 4, and 100% in year 5 and beyond, based on the same assumptions used in TA534 for AD. For a sensitivity analysis, the company used estimates based on their SEE exercise, where the elicited expert responses indicated a faster decline in adherence to BSC in PN compared to AD, but with some patients expected to maintain response beyond two years, which was carried forward for year 3 and onwards. The resulting estimates used in the sensitivity analysis were [redacted] in year 2 and [redacted] in year 3 and beyond.

Points for critique

The EAG has a number of concerns relating to the extrapolation assumptions used to model long-term treatment effectiveness. First, the EAG is not entirely clear why *both* an all-cause annual treatment discontinuation rate (that includes loss of treatment response) and a probability of sustained response per year is used to model long-term response to treatment (both of which are implemented as a transition probability [additively] from the 'Response' to 'No response' treatment state in the model).

The company states that the all-cause discontinuation rate is used to model loss of response, adverse events or patient/clinician preference, while the concept of response waning is used to model the exit from the controlled clinical trial environment where the observed effect size for BSC alone would not persist once patients have completed the trials and are outside the protocol-driven clinical trial setting. The EAG is not clear why these further discontinuations associated with response waning are applied on top of the annual discontinuation rate, as the purpose of the model is to reflect standard NHS clinical practice, where the decision to implement either dupilumab plus BSC or BSC alone is not based on patients having previously exited a clinical trial setting before commencing treatment.

If the main purpose of the response waning is to account for the high response rates seen in the placebo arm of the trials due to improved adherence to BSC treatment that is unlikely to be sustainable for a prolonged period of time outside a clinical trial setting, then any benefit from improved adherence would be expected to be applied equally to both the dupilumab plus BSC and BSC alone arms of the clinical trials, which should not affect how the treatments perform relative to one another. Note that the company have also adjusted down the utility values for patients who become non-responders (having previously responded to treatment at week 24) at three time points (6 months, 1 year and ≥2 years based on the results of the SEE exercise) to reflect the exit from the protocol-driven environment of the PRIME2 and PRIME trials and the return to real-world clinical practice (see Section 4.2.8.4). This means that both a response waning effect (affecting the movement of patients from the 'Response' to 'No response' states) and a waning of health-related quality of life for non-responders to treatment is included in the model to account for lower adherence to BSC in clinical practice.

The implications of a very high annual discontinuation rate for BSC ([redacted]), and a low probability of sustaining response over time (100% loss by year 5, with rapid loss in previous years) 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, with everyone on BSC assumed to be non-responders very quickly (incurring lower utility and higher resource use and costs associated with non-response to treatment). This can be observed in the Markov trace for the proportion of responders and non-responders to treatment over time (see **Error! Reference source not found.** and Figure 4 for dupilumab plus BSC and BSC alone, respectively). Importantly, it means that the *relative* difference in the response rates observed in the pooled PRIME2 and PRIME trials for dupilumab plus BSC compared to BSC alone at week 24 for the different response criteria (Table 12 and Table 13 above) is less important for the cost-effectiveness of dupilumab plus BSC than the *absolute* value for the response rate in the dupilumab plus BSC arm of the trials because the response rate for BSC rapidly falls to 0% due to the high discontinuation rate and response waning assumptions used for BSC.

item 7. The EAG does not consider it appropriate to include both an all-cause annual treatment discontinuation rate (that includes loss of response over time) and a probability of sustained response per year, for responders in the model.

Figure 3 Markov trace showing the proportion of responders and non-responders to dupilumab plus BSC over time

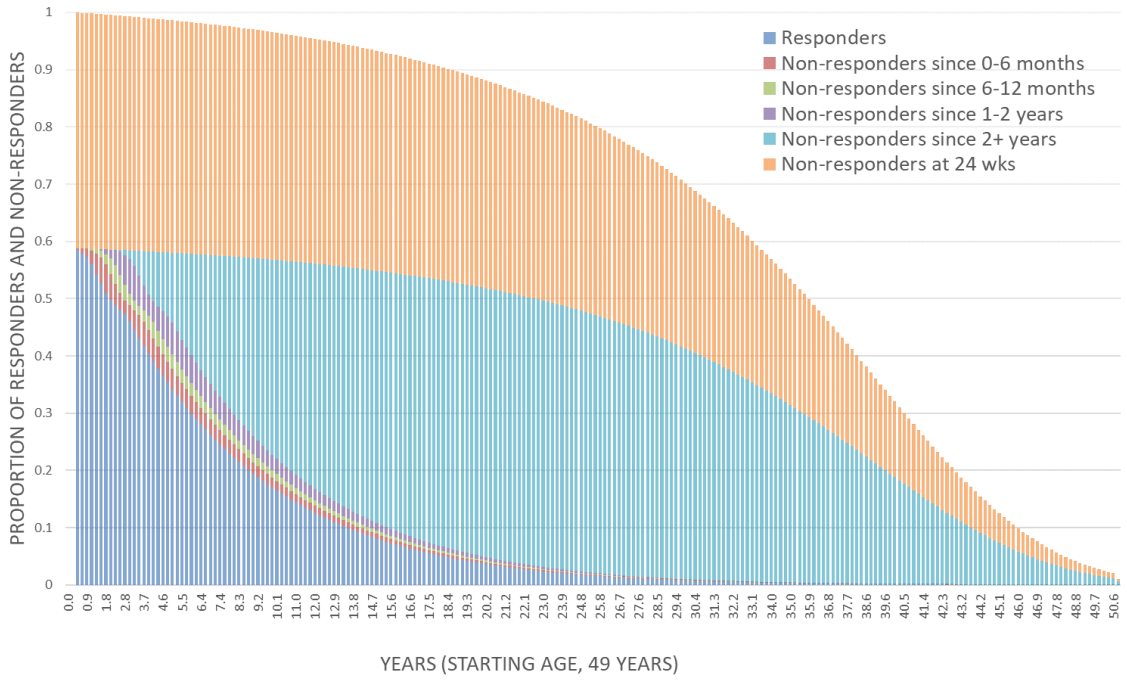
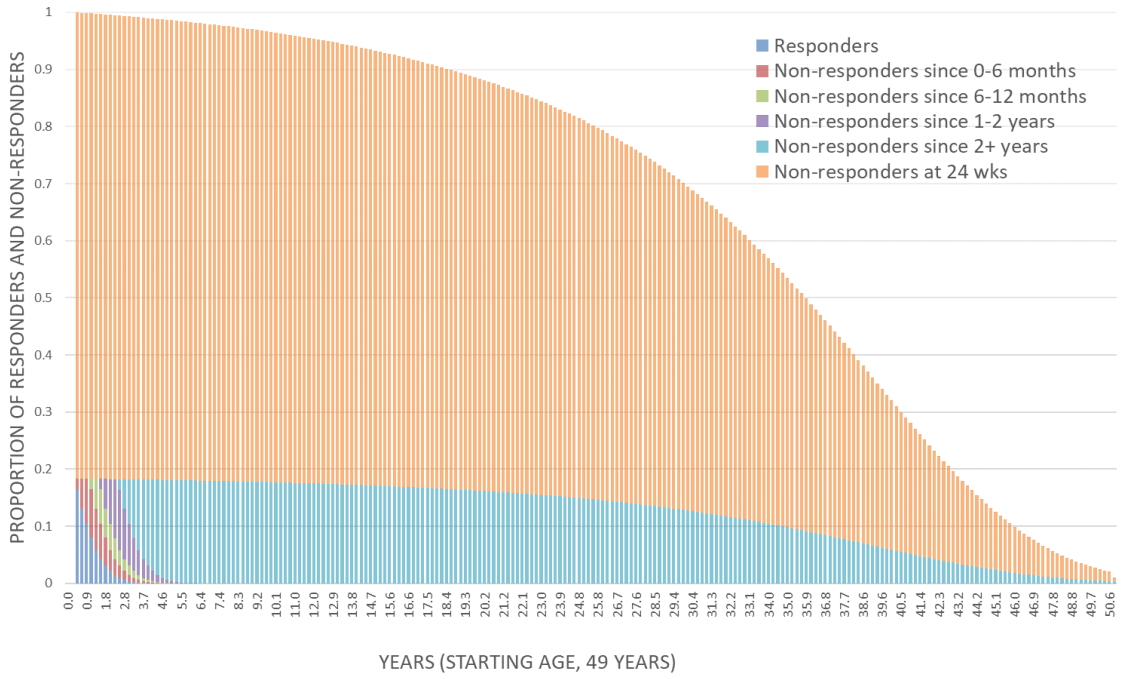


Figure 4 Markov trace showing the proportion of responders and non-responders to BSC alone over time



The second concern relates to the source of evidence used to inform the annual all-cause treatment discontinuation rates used in the model. The model uses the pooled all-cause treatment discontinuation rates from the PRIME2 and PRIME trials over a 24-week period as a proxy for the loss of response over the modelled time horizon, which results in differential annual discontinuation rates for dupilumab plus BSC of [redacted] and BSC alone of [redacted]. The EAG has three main issues with using the trial evidence as a proxy for long-term response:

(i) The discontinuation rate for loss of response in the trials is already reflected in the percentage of responders to treatment at week 24;

(ii) There is expected to be improved adherence to treatment and access to healthcare facilities and professionals in the protocol-driven clinical trial setting, which are unlikely to be mirrored outside the trial setting;

(iii) The treatment discontinuation rate for dupilumab plus BSC is very low.

These concerns are in addition to the more general concern regarding the generalisability of the PRIME2 and PRIME trials to UK clinical practice.

The EAG considers that the treatment-specific discontinuation rates used in the model are highly uncertain given the lack of evidence on treatment stopping rules, or persistence of effect over the long-term, from either trial extension or observational studies, or data from registries that reflect NHS

clinical practice. This is further exacerbated by the fact that the treatment regimens used in the placebo arm of the PRIME trials are unlikely to match that used for BSC in UK clinical practice.

item 8. The annual treatment discontinuation rates are highly uncertain due to short trial follow-up and limited evidence.

The third concern relates to the source of evidence used to inform the response waning assumptions for both dupilumab plus BSC and BSC alone. For dupilumab plus BSC, the company adjusted down the proportion of people who respond to treatment over time (i.e., moved to treatment with BSC only and accrued the utility associated with dupilumab plus BSC non-responders) using data from an ongoing, open-label extension (OLE) study assessing the long-term safety and efficacy of dupilumab in adults with moderate-to-severe AD.[22] Out of 2,678 participants enrolled in this study, 352 participants were assessed for sustained efficacy at week 204 (up to 3.92 years follow-up), with missing data not imputed. The EAG has concern about the applicability of using long-term efficacy data for dupilumab in AD as a proxy for the probability of sustained response for dupilumab plus BSC in PN. Although the two diseases share similarities, being type 2 inflammatory skin diseases, the primary efficacy endpoint used in the study for AD was the proportion of participants achieving EASI-75 (Eczema Area and Severity Index) outcome at week 100 (91.4%), week 148 (97.2%) and week 204 (90.9%), which is used in the company's model in PN for the probability of sustained response in year 2, year 3, and year 4+, respectively. The EAG does not consider the outcome of EASI-75 to be relevant for PN. The EAG notes that the proportion of patients achieving ≥4-point reduction in weekly Pruritus Numerical Rating Scale (NRS) score from baseline at week 100 (65.7%), week 148 (64.8%) and week 204 (70.8%) from this study may be a more relevant outcome for PN because it provides a measure of itch intensity. The EAG considers a scenario in Section 6 that assesses the cost-effectiveness of dupilumab plus BSC relative to BSC alone using alternative values for the probability of sustained response in year 2 (65.7%), year 3 (64.8%), and year 4+ (70.8%) based on using the proportion of patients achieving ≥4-point reduction in weekly Pruritus NRS score in AD as a proxy for WI-NRS in PN.

For BSC alone, the company adjusted down the proportion of responders to BSC over time using assumptions from TA534 for AD, where a rapid loss of clinical benefit was considered of 25%, 50%, 75% and 100% in years 2, 3, 4 and 5+, respectively. This downward adjustment, in addition to the high annual discontinuation rate of [redacted] for responders to BSC, means that the response rate for BSC falls rapidly to 0% by year 3. The EAG notes that in TA534 the estimates of 25% (year 2), 50% (year 3), 75% (year 4) and 100% (year 5+) were used to adjust down the utility value applied over time such that by the end of year 5, everyone in the BSC arm returned to the baseline utility for the remainder of their time in the model. In contrast, in the company's model for PN, it is the proportion of responders that is adjusted downwards over time, incurring lower utility values (based on time

since discontinuation due to loss of response and higher resource use and costs associated with non-response). The appraisal committee for TA534 concluded that there was uncertainty surrounding the assumptions on loss of utility benefit for BSC in AD and that the company's base case assumptions that used 25% (year 2), 50% (year 3), 75% (year 4) and 100% (year 5+) were less plausible that those presented in two sensitivity analyses based on 'time to rescue therapy/stopping study' projections from the CHRONOS trial in AD; sensitivity analysis 1 used 82% (year 2), 90% (year 3), 94% (year 4) and 96% (year 5+), while sensitivity analysis 2 used 57% (year 2), 82% (year 3), 92% (year 4) and 97% (year 5+).[5] The company did, however, conduct a sensitivity analysis based on estimates derived from their SEE exercise in PN, which used much lower values for the loss of response on BSC of [redacted]% for year 2 and [redacted] for year 3 and beyond. This sensitivity analysis demonstrated that the cost-effectiveness results were not sensitive to the response waning assumptions used for BSC over time (CS, p110). However, the EAG notes that the results were not sensitive for two reasons: (i) a very high annual discontinuation rate of [redacted] is still assumed for responders to BSC, which means that most patients have already moved to the 'No response' state; and (ii) the model results are more sensitive to the utility difference between dupilumab plus BSC non-responders and BSC alone non-responders at week 24 than the utility difference between dupilumab plus BSC responders and BSC responders.

item 9. The probabilities of sustained response over time for both dupilumab plus BSC and BSC alone are highly uncertain due to short trial follow-up and limited evidence.

At points for clarification, the EAG requested data for each treatment arm on the percentage of responders to treatment at week 36 (end of study) after the 12-week post-treatment follow-up period of the PRIME2 and PRIME trials, in order to give an indication of the loss of response after treatment withdrawal (noting that no data from the 12-week post-treatment follow-up period of the trials had been presented in the company's original submission). The company provided data on the proportion of participants with response at week 36 according to their response at week 24 for the pooled ITT population for the following criteria (see Appendix 1 of company response to EAG points for clarification):

- WI-NRS improvement (reduction) ≥ 4 points;
- IGA PN-S score 0 or 1;
- Both WI-NRS improvement (reduction) ⩾ 4 points and IGA PN-S score 0 or 1;

A summary of the data on persistence of response at week 36 for responders and non-responders to treatment at week 24 is presented in Table 14. Although a significant proportion of the data is missing, the limited data available appears to suggest [redacted]

[redacted]

Table 14 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]

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.
†Excludes participants requiring rescue therapies (censored from the primary endpoint analysis of the trials).

4.2.6.3 Mortality

All-cause mortality is estimated based on National Life Tables for the UK.[23] The model assumes patients do not have an increased risk of mortality due to PN, which the EAG considers to be appropriate.

4.2.7 Adverse events

4.2.7.1 Summary of company's submission

The AEs considered in the model are based on those reported in the PRIME2 and PRIME clinical trials. AEs are assumed to be incurred at every model cycle, rather than being incurred as one-off costs at treatment initiation. In the model, costs of AEs are considered but disutilities due to AEs are not included because AEs arising from treatment during the trials are assumed to be mild and transient. The costs of AEs are summarised in **Error! Reference source not found. Error! Reference source not found.**.

4.2.8 Health related quality of life

4.2.8.1 Summary of company's submission

Health state utility values are applied to time spent in health states in the model, in order to calculate quality-adjusted life years (QALYs) that reflect the improvement in health-related quality of life (HRQoL) associated with treatment. The company undertook a literature review to identify studies assessing the HRQoL of patients with PN (see Appendix H of the CS for full details about the systematic literature review, including methodology, study selection process, inclusion and exclusion criteria and results) – See Appendix 1 for EAG critique of literature search. There were no studies that generated EQ-5D utility values in patients with moderate-to-severe PN. Instead, the company provides an analysis of EQ-5D data from the PRIME2 and PRIME trials, the company have presented analyses of these data in their submission.

The CS summarises data collected in the PRIME2 and PRIME trials using the DLQI and EQ-5D-5L instruments and considers this data to represent the best available HRQoL and utility data for patients with moderate-to-severe PN, whose disease is inadequately controlled with topical prescription therapies. Therefore, the trial-based utilities are used to inform the company's model.

The CS describes four elements relating to the quantification of HRQoL: (i) short-term (within-trial) utility values for the first 24 weeks; (ii) derivation of utility values for use in the model; (iii) extrapolation of utility values over time; and (iv) adjustment of utility values by age.

4.2.8.2 Short-term (within-trial) utility values

Data are collected from the PRIME2 and PRIME trials at three specific timepoints (baseline, week 12, and week 24) using the EQ-5D-5L instrument and valued using a UK tariff are presented in Table 15. Two algorithms[18, 19] were used to convert the five-level EQ-5D instrument into the three-level EQ-5D (EQ-5D-3L), in line with the NICE methods guidance manual,[21] with Hernández Alava algorithm used for the base case analysis and van Hout used in a sensitivity analysis.

Table 15 EQ-5D single index score in the pooled ITT population (reproduced from CS Table 27, p83)

	EQ-5D-5L from pooled PRIME2 and PRIME trials.		**Conversion to EQ-5D-3L with UK crosswalk tariffs (Hernández Alava 2020; base case).**		**Conversion to EQ-5D-3L with UK crosswalk tariffs (van Hout 2012; sensitivity analysis).**	
	BSC	**Dupilumab plus BSC**	**BSC**	**Dupilumab plus BSC**	**BSC**	**Dupilumab plus BSC**
Baseline	**N=156**	**N=153**	**N=156**	**N=153**	**N=156**	**N=153**
Mean (SD)	0.640 (0.258)	0.621 (0.261)	0.662 (0.257)	0.643 (0.262)	0.640 (0.258)	0.621 (0.261)
Median	0.725	0.725	0.722	0.723	0.725	0.725
Week 12	**N=153**	**N=152**	**N=153**	**N=152**	**N=153**	**N=152**
Mean (SD)	0.72 (0.20)	0.76 (0.22)	0.735 (0.206)	0.766 (0.214)	0.724 (0.204)	0.758 (0.215)
Median	0.77	0.79	0.762	0.791	0.767	0.787
Week 24	**N=145**	**N=152**	**N=145**	**N=152**	**N=145**	**N=152**
Mean (SD)	0.72 (0.22)	0.76 (0.22)	0.729 (0.218)	0.779 (0.218)	0.721 (0.221)	0.765 (0.220)
Median	0.77	0.80	0.784	0.817	0.768	0.796

Abbreviations: BSC: best supportive care; EQ-5D-3L: Euroqol 5-dimension 3-level; EQ-5D-5L: Euroqol 5-dimension 5-level; ITT: intent-to-treat; SD: standard deviation; UK: United Kingdom.

Points for critique

The EAG considers the approach used by the company to be appropriate and in line with the updated 2022 NICE evaluation methods manual.[21] The EAG agrees that the data from the pooled PRIME2 and PRIME trials represent the best available source of utility data to inform the model.

4.2.8.3 Derivation of utility values for use in the model

The utility values used in the model based on response to treatment were derived from mixed (repeated measures) regression models that used the EQ-5D-5L utility score as the response variable after controlling for baseline age, gender, EQ-5D-5L utility weight, and DLQI score, and included the following predictor variables: DLQI total score, WI-NRS score, IGA-PN-S score, the interaction between WI-NRS score and DLQI total score, and an indicator variable for treatment allocation. In a forward selection process, significant variables were kept in the regression, and goodness-of-fit was assessed using diagnostic plots, Akaike information criterion (AIC), and the Bayesian information

criterion (BIC) statistics, where lower AIC and BIC values indicate better fit (see Figures 16 and 17, p85-86 of the CS). The regression models showed that most of the treatment effect was captured by the DLQI and WI-NRS follow-up scores (see Table 28, p84 of the CS for the resulting regression model coefficients).

Utility weights for application in the model were generated by multiplying the coefficients from the mixed regression models by the mean baseline characteristics and mean DLQI and WI-NRS scores (estimated by adding mean change from baseline scores) of the base case population (the average population characteristics of the PRIME2 and PRIME trials). The treatment indicator was also applied and follow-up scores at week 24 distinguished between responders and non-responders in order to generate treatment arm specific utility weights, stratified by response to treatment at week 24. Table 16 summarises the utility values used in the model. In the decision tree model, the baseline utility (pooled across treatment arms) is used from baseline to week 12, whilst the utility value by treatment arm at week 12 (not separated by response) is used from week 12 to week 24. At the end of the decision tree, when response to treatment is assessed, separate treatment arm utility values are used for responders and non-responders.

Table 16 Utility values used in the company's base case analysis

	Baseline	Pooled response		Separate response			
		Week 12†		Week 24			
				Responders		Non-responders	
	Pooled arms*	Dupilumab plus BSC	BSC	Dupilumab plus BSC	BSC	Dupilumab plus BSC	BSC
Utility values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care.
*For pooled arms, a weighted average of utility values in each treatment arm is used in the model.
†Week 12 utility values are used from week 12 to week 24 in the decision tree model.

Points for critique

The EAG considers the general regression-based approach used by the company to be appropriate, in light of the correlation between clinical measures of disease burden and HRQoL outcomes in PN. The EAG has no major concerns with the methods used, however it notes that limited details are presented on the imputation method (MI) used for dealing with missing trial participant data.

The EAG wishes to highlight a number of key points in relation to the utility values applied in the model:

- A larger proportion of the HRQoL improvement from baseline is achieved at week 12 relative to that achieved at week 24, for both treatment arms.

- The difference in utility between dupilumab plus BSC and BSC alone at week 12 ([redacted]) is larger than the difference between treatment arms at week 24 for responders ([redacted]) or non-responders ([redacted]).
- There is a much larger difference in utility weights between dupilumab plus BSC and BSC alone in non-responders at week 24 ([redacted]) compared to differences between treatment arms in responders at week 24 ([redacted]).

Of these points, the EAG has a concern that most of the HRQoL improvement associated with treatment, as observed in the PRIME2 and PRIME trials, is a result of better adherence to treatments in the protocol-driven clinical trial setting for both treatment arms. The CS makes a strong case for this effect in the BSC arm, noting that it would not be possible to sustain the treatment effect from BSC on HRQoL at the levels observed in the trials once participants leave the protocol-driven clinical trial setting; however, the CS states that the dupilumab response is derived from the clinical benefit of receiving an active biologic substance. The EAG notes that a large difference in HRQoL is not observed between treatment arms in responders to treatment and, in fact, a larger difference between treatment arms is observed in participants who did not respond to either treatment by week 24. The EAG is not clear why a difference in HRQoL would be expected between treatment arms in non-responders to treatment. Furthermore, as noted in Section 4.2.6.2.,

[redacted] In the company's model, the pooled (across treatment arms) week 24 estimates of utility for non-responders ([redacted]) is provided, but this not used in the model.

The EAG believes that the pooled (across treatment arms) week 24 utility value for non-responders would be more appropriate for all non-responders in the model at week 24 because these patients have not responded to treatment and therefore they are not getting any active benefit from treatment, dupilumab plus BSC or BSC alone. Furthermore, the model assumes that once patients become non-responders to dupilumab plus BSC they receive BSC only. Therefore, it would seem implausible to apply two separate utility values for non-responders by treatment arm when all non-responders receive BSC only in the model

[redacted]. The EAG notes that it could be argued that the utility value for BSC non-responders ([redacted]) should be used for all non-responders because they receive BSC only. The EAG conducted Scenario 7-8 in Section 6.1.1.6; one that uses the pooled (across treatment arms) week 24 utility value for non-responders ([redacted]), and the other that uses the week 24 utility value for BSC non-responders ([redacted]) for all non-responders in the model in order to assess the implications for the cost-effectiveness of dupilumab plus BSC.

item 10. The EAG does not consider it appropriate to apply separate utility values by treatment arm for non-responders because all non-responders receive BSC only in the model, and any treatment effect is expected to diminish upon discontinuation of treatment.

4.2.8.4 Extrapolation of utility values over time

Since there are no extension studies to provide data on the real-world effectiveness of dupilumab plus BSC or BSC alone in PN the company conducted a structured expert elicitation (SEE) to elicit how HRQoL might evolve in the short and longer term for patients with PN, after they leave the protocol-driven environment of the PRIME2 and PRIME trials and return to real-world clinical practice. The experts provided input on the proportion of HRQoL maintained after trial completion at three distinct time points (6 months, 1 year and 2+ years) for four groups of patients: (i) dupilumab responders, who responded to treatment during the trial but subsequently discontinued dupilumab treatment at some point after the end of the trial; (ii) dupilumab non-responders, who did not respond to treatment or lost their response by the end of the trial and discontinued dupilumab treatment; (iii) BSC responders, who responded to treatment during the trial; and (iv) BSC non-responders, who did not respond to treatment or lost their response by the end of the trial. The proportion of HRQoL maintained for dupilumab responders that remain on treatment was not considered on the basis that their response to treatment would persist over time until discontinuation according to clinician input. Therefore, health-related quality of life improvements for responders at week 24 are maintained for patients responding to treatment over time until treatment discontinuation, i.e., the utility value of [redacted] for dupilumab plus BSC responders is held constant over time in the model until treatment discontinuation.

Results from the elicitation suggest that nearly all HRQoL benefits accrued within the PRIME2 and PRIME trials would be lost after leaving the trials for all dupilumab plus BSC patients and BSC patients who discontinued treatment, but the rate of decline and plateau point are dependent on treatment arm and response (Table 17**Error! Reference source not found.**). The rate of decline is faster in the BSC arm compared to the dupilumab arm and in non-responders versus responders, while the plateau point is higher in responders versus non-responders. The results also show that patients would be close to baseline utility, or worse (in the case of BSC non-responders), at two years' post-trial and beyond.

Table 17 Proportion of utility maintained at each time interval from the company's structured expert elicitation (reproduced from CS Table 21, page 77)

Subgroup	Time point[a]	Median (50th percentile)	IQR (25th-75th percentile)	95% CrI (5th-95th percentile)
Dupilumab responders, %	**6 months**	38%	27%-48%	20-59%
	1 year	18%	14%-25%	10%-39%
	2+ years	9%	6%-12%	3-%16%
Dupilumab non-responders, %	**6 months**	20%	11%-25%	8%-42%
	1 year	5%	1%-13%	-2%-18%

Subgroup	Time point[a]	Median (50th percentile)	IQR (25th-75th percentile)	95% CrI (5th-95th percentile)
	2+ years	0%	-7%-8%	-15%-13%
BSC responders, %	**6 months**	29%	22%-38%	16%-49%
	1 year	15%	12%-19%	5%-25%
	2+ years	9%	2%-14%	-2%-17%
BSC non-responders, %	**6 months**	10%	6%-16%	3%-20%
	1 year	1%	-1%-11%	-3%-16%
	2+ years	0%	-9%-6%	-12%-9%

Abbreviations: BSC: best supportive care; CrI: credible interval; IQR: interquartile range.
[a]For dupilumab responders, the time point is the time-post-treatment discontinuation, while for all other subgroups, the time point is the time-post-trial completion.

The SEE results in Table 17 were used by the company to adjust down the utility weights applied over time for *non-responders* to treatment in the model. In the dupilumab plus BSC arm of the model, a proportion of patients, who responded to treatment at week 24, are assumed to lose response over time according to the response waning assumptions outlined in Section 4.2.6.2, discontinue dupilumab treatment and move to the 'No response' state, where they receive BSC only. These patients then become classified as dupilumab plus BSC non-responders in the model, and the model keeps track of their time since discontinuation via a series of tunnel states. When response is lost, the difference in utility between dupilumab plus BSC *non-responders* at week 24 ([redacted]) and baseline utility ([redacted]) is adjusted down by the percentage of utility maintained for dupilumab responders from the SEE (median value) at each time interval, i.e., 38% for 6-12 months since discontinuation, 18% for 1-2 years since discontinuation, and 9% for 2 years and more since discontinuation, then added to the baseline utility value in order to estimate the utility weight for dupilumab plus BSC non-responders according to time since dupilumab discontinuation. In a similar manner, in the BSC arm of the model a proportion of patients, who responded to treatment at week 24, are assumed to lose response over time and move to the 'No response' state but, unlike dupilumab responders, they do not discontinue treatment (remain on BSC). When BSC response is lost, the difference in utility between BSC *non-responders* at week 24 ([redacted]) and baseline utility ([redacted]) is adjusted down by the percentage of utility maintained for BSC *non-responders* from the SEE (median value) at each time interval, i.e., 10% for 6-12 months since discontinuation, 1% for 1-2 years since discontinuation, and 0% for 2 years and more since discontinuation, then added to the baseline utility value in order to estimate the utility weight for BSC non-responders according to time since lost response to BSC. Table 18 summarises the utility values used in the company's base case analysis for non-responders to treatment over time according to time since becoming a non-responder (i.e., time since discontinuation of dupilumab for dupilumab plus BSC arm and time since lost BSC response for BSC alone arm because BSC patients do not discontinue treatment).

Table 18 Utility values used in the company's base case analysis for non-responders to treatment over time according to time since becoming a non-responder

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.
*Assumed to have the same utility value as non-responders at week 24 from the pooled trials.
†Close to baseline utility value.

Points for critique

The EAG has a number of concerns regarding the approach used by the company to extrapolate utility values over time. The first concern relates to both the appropriateness and credibility of the results of the SEE for informing how HRQoL might evolve over the long-term for patients with moderate-to-severe PN when treated with either dupilumab plus BSC or BSC alone in NHS clinical practice. The SEE was used to elicit the proportion of HRQoL maintained for patients with PN, after they leave the protocol-driven environment of the PRIME2 and PRIME trials and return to current real-world clinical practice. However, as noted previously, the EAG considers that the decision to implement either dupilumab plus BSC or BSC alone in the NHS is not based on patients having previously exited a clinical trial setting before commencing treatment. Therefore, the emphasis placed on how HRQoL evolves after patients complete the trial and return to current real-world clinical practice seems less relevant than how response rates and HRQoL might evolve over time after achieving response or no-response to treatment at week 24.

The approach to elicitation was in line with the structured expert elicitation resources (STEER) guidance.[24] This method aims to minimise bias associated with eliciting subjective judgements. A number of principles, suggested by the STEER framework, where adhered to in the company's elicitation exercise. Specifically: only substantive experts were recruited using a pre-specified recruitment and selection criteria, the experts were trained prior to the task, including awareness on forms of bias, the draft elicitation was piloted with a substantive expert, a SEE protocol was developed and rationales were elicited following each quantity elicited.

A number of observations can be made regarding the methods employed in the SEE and the likely credibility of the resulting elicited estimates:

- Six experts were contacted to take part in the SEE, however only four completed the task, with only three experts included in the pooled analysis. The description of why these two experts were not included states that during an internal validation step, the resulting distributions of two experts did not match the experts' judgements as suggested in their qualitative feedback. After a communication with these experts, it was apparent that their answers reflected patient variability rather than subjective uncertainty surrounding the average. One expert provided new valid estimates and was therefore included in the quantitative summary; however, the final expert was unresponsive and therefore their original estimates were excluded. This may suggest that the training provided to experts was not sufficient to ensure that experts focussed on uncertainty regarding the mean as opposed to variability between patients.
- Judgements were elicited individually from experts using an online survey. The bisection method was used to determine uncertain judgements. The bisection approach uses a variable interval method; 1%, 99% and 50% percentiles. This is an alternative to the fixed interval methods. The STEER guidance concludes that either approach is appropriate for SEE to inform health care decision making.
- Individual judgements were then pooled using unweighted linear opinion pooling, therefore implicitly assuming equal weights for all experts. Linear opinion pooling is an approach recommended for quantities where independence can be assumed. The quantities elicited, however, are unlikely to be independent as these constitute the proportion of HRQoL maintained at 6-months, 1-year and $\geqslant$2 years post-enrolment in the PRIME2 and PRIME trials. For each expert the proportion expressed at each of these time points will be contingent (conditional) on the proportion expressed at other time points. It is not clear that this relationship between time points was made explicit in the questions posed to experts, i.e., phrasing the questions such that "conditional on the previous time point what percentage of HRQoL is maintained".
- The analysts designing the SEE recognised that HRQoL is unlikely to be observed by the clinical experts participating in the task. In order to overcome this, they elicited relative changes (percentage maintained) compared to the values observed in the trials. The issue remains that experts are unlikely to have substantive experience in understanding what a percentage change in HRQoL translates into in clinical practice.

Additional limitations associated with the SEE are outlined in the CS, Section B.3.3.2.2.5 on page 79.

item 11. The credibility of the results of the SEE for informing how HRQoL might evolve over the long-term for patients with moderate-to-severe PN when treated with either dupilumab plus BSC or BSC alone in NHS clinical practice is unclear.

The second key concern for the EAG is the methods used to adjust down the utility weights applied over time based on the results of the SEE. The EAG notes a number of inconsistencies in the approach used by the company:

- The utility weight for patients who lose treatment response with dupilumab plus BSC and become non-responders in the model, having previously responded to treatment at week 24, i.e., those classified as dupilumab responders in the SEE (Table 17), is based on adjusting down the difference in utility between dupilumab plus BSC non-responders at week 24 and baseline utility rather than the difference in utility between dupilumab plus BSC *responders* at week 24 and baseline utility, since these patients were previous responders to treatment. Applying the downward adjustment to the change in week 24 utility for dupilumab plus BSC non-responders is inconsistent with the application of the percentage of utility maintained for dupilumab responders from the SEE at each time interval, i.e., 38% for 6-12 months since discontinuation, 18% for 1-2 years since discontinuation, and 9% for 2 years and more since discontinuation.
- The utility weight for BSC patients who lose response to BSC and become non-responders in the model, having previously responded to BSC at week 24, i.e., those classified as BSC responders in the SEE (Table 17), is based on adjusting down the difference in utility between BSC non-responders at week 24 and baseline utility rather than the difference in utility between BSC *responders* at week 24 and baseline utility, since these patients were previous responders to treatment. In other words, treatment waning for BSC should be applied through loss of utility gain associated with *response* at week 24. Furthermore, the downward adjustment to the change in week 24 utility for BSC responders should be based on the percentage of utility maintained for BSC *responders* from the SEE at each time interval, i.e., 29% for 6-12 months since loss of response, 15% for 1-2 years since loss of response, and 9% for 2 years and more since loss of response. Instead, the company have applied the percentage of utility maintained for BSC non-responders from the SEE.
- The utility weight for dupilumab plus BSC non-responders, who did not respond to treatment by week 24 in the trials, is *not* adjusted down in accordance with the results of the SEE, i.e., the results of the SEE for those classified as dupilumab non-responders in the SEE (Table 17) are not used. Instead, the utility weight for dupilumab plus BSC non-responders at week 24 in the model is adjusted down over time using the percentage of utility maintained for dupilumab responders from the SEE at each time interval, i.e., 38% for 6-12 months since becoming non-responders, 18% for 1-2 years since becoming non-responders, and 9% for 2 years and more since becoming non-responders. In contrast, the utility weight for BSC non-responders, who did not respond to treatment by week 24 in the trials, is adjusted down based on the results of the SEE for those classified as BSC non-responders in the SEE (Table 17).

The EAG is unclear about the justification for the inconsistencies in the approach used by the company to downward adjust the utility values for non-responders. Importantly, the EAG notes that the utility values for dupilumab plus BSC non-responders when they move to BSC remain higher than the utility values for BSC, even after 5+ years loss of treatment response. The utility values and their extrapolation over time is one of the key drivers of the cost-effectiveness results. Therefore, the EAG explores the impact of a number of alternative scenarios for the utility values in Section 6, including a scenario where the inconsistencies in the company's approach based on the results of the SEE are removed and a scenario where the utility value of non-responders only holds constant for the first 6 months after treatment discontinuation and then rebounds to baseline utility from month 6 onwards.

item 12. The EAG identified a number of inconsistencies in the company's approach to adjusting the utility values based on the results of the structured expert elicitation.

4.2.8.5 Adjustment of utility values by age

Age adjustments were made to the utility values over time by applying the multiplicative method to the general population utility weights from Ara et al., 2017[25] to estimate the relative decline over time. The EAG considers the approach used by the company to be appropriate.

4.2.9 Resource use and costs

4.2.9.1 Summary of company's submission

The CS includes costs related to (i) drug acquisition and administration; (ii) rescue medication; (iii) disease management; (iv) adverse events; and (v) productivity loss (not included in company's base case analysis). Unit costs were informed by national public sources and previous NICE guidance, inflated to 2020/21 prices where appropriate and discounted at an annual rate of 3.5%.

Table 19 Costs used in the company's base case analysis

Item	Model input	Source
Drug acquisition costs per year		
Dupilumab	first year: [redacted] subsequent years: [redacted]	Calculated based on the dosing of dupilumab in PN: an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week by subcutaneous injection. The annual cost for dupilumab considering list price is £16,500 per patient per year. Includes confidential PAS discount ([redacted]) for dupilumab (confidential price is [redacted]).
BSC	TSC £ 912 TCI £ 545 (Total cost = £ 1,457)	The average acquisition costs of TCS and TCI are estimated based on the British National Formulary (see CS Table 39, 40 p98). TCS cost is calculated based on the average cost of all preparations being used in equal proportions. TCI cost is based on the use of tacrolimus.

		The treatment frequency of TSC is 100g every two weeks, and TCI is 100g every six weeks. The estimations of treatment frequency are presented in CS Table 41, p98.
Administration costs (one-off cost)		
Self-injection training by hospital nurse for dupilumab	£ 55	Calculated based on clinical practice for AD, it is assumed that dupilumab patients receive a one-hour subcutaneous self-injection training once by a hospital nurse and self-administer thereafter.
Rescue medication costs per year		
Dupilumab plus BSC	£ 1.52	The cost of rescue medications is estimated according to the category and frequency of medications used by participants in the PRIME2 and PRIME trials. The average acquisition costs of each medication was based on the British National Formulary and presented in CS Table 42, p99. Treatment duration for each medication is assumed to be 14 days, except in cases where the drug would be expected to require more than 14 days to take effect, or the British National Formulary dose is incompatible with a 14-day course.
BSC	£ 56.12	
Disease management costs per year		
Responders	£ 1,359	Calculated based on treatment response status. Responders are assumed to incur reduced disease management costs. Calculated by multiplying the frequency of use of each healthcare resource for responders and non-responders (see CS Table 35 p95) by the unit price of each resource (see CS Table 43 p100).
Non-responders	£ 2,952	
Adverse event costs per year		
Dupilumab plus BSC	£ 36.46	Calculated based on AEs reported in the PRIME2 and PRIME trials. The unit costs and the incidence of these events for the PRIME2 and PRIME trials are shown in the CS Table 45 p102. Patients who received BSC only were assigned the AE cost of BSC. Patients who received two therapies (e.g., dupilumab plus BSC) only incurred one AE cost. They were assigned the more expensive of the two AE costs, if applicable.
BSC	£ 3.22	

Abbreviations: BSC: best supportive care; PN: prurigo nodularis; PAS: patient access scheme; AE: adverse event; TCS: topical corticosteroids; TCI: topical calcineurin inhibitors; PPPY: per patient per year; AD: atopic dermatitis.

Disease management costs

Disease management costs depend on response status. Three activities were undertaken by the company to identify resource utilisation rates and unit costs:

1. A systematic literature review to identify costs and healthcare resource use data associated with PN. The review did not identify any studies reporting costs and resource use data in England or the UK (details of the methodology, study selection process, inclusion and exclusion criteria and results are presented in Appendix I of the CS) – see Appendix 1 for EAG critique of literature search.

2. A retrospective cohort burden of illness (BOI) study to understand the health care resource utilisation (HCRU) of patients with moderate-to-severe PN in England.[20] Patient data were derived from the CPRD GOLD and Aurum primary care datasets linked to HES, examining records between 2007 and 2019. This identified 8,933 patients with PN, of which 2,498 (28%) required systemic treatment and were classified as having moderate-to-severe PN. Patients with moderate-to-severe PN were matched 1:1 (age and gender) to patients with mild PN in order to compare the rates of HCRU associated with the two subpopulations (see CS Table 33, p92).
3. Advisory board to validate UK clinicians' perceptions of HCRU among patients with moderate-to-severe PN who may be candidates for dupilumab (included two UK clinicians and one health economics and outcomes research expert). The two clinicians were asked to consider the resource use values from the retrospective BOI study and the resource use that was accepted by NICE in TA534 for AD and use it to assess resource use for responders and non-responders to treatment in moderate-to-severe PN, in terms of consultant dermatology visits, general practitioner visits, accident & emergency visits and hospital in-patient stays (see CS Table 34, p93 for the proposed annual HCRU values from the two UK clinicians).

The CS synthesised all available sources of resource use data for patients with moderate-to-severe PN in order to derive an annual number of resource use units (frequency of use) by responders and non-responders to treatment. Table 20 presents the resource use data for responders and non-responders used in the company's base case analysis, alongside the rationale. HCRU values from TA534 and TA814 are used in sensitivity analyses by the company.

Table 20 HCRU values used in the model (reproduced from CS Table 35, p95)

	Resource use frequency per patient year		Source and justification
	Responder	**Non-responder**	
Primary care visit	2.00	11.00	UK advisory board;[4] Note the company states that these values are conservative because they are lower than in the retrospective BOI study in England (mild PN: 11.35; moderate-to-severe PN: 21.27).[20] Mid-point between clinician estimates (CS Table 34 p93) and the BOI study. Clinicians stated consultations could be 10–12 per year based on additional remote consultations.
Dermatologist outpatient visit	2.00	5.00	Synthesis of best available evidence including UK advisory board[4] plus the retrospective BOI study in England[20] (taking into account the value for 'outpatient visit (any speciality)' and accounting for challenges with proper patient diagnosis and coding; CS Table 33 p91). Based on clinician input that the number is likely between four to six visits per year, five visits has been chosen as the mid-point in this range.[4]

	Resource use frequency per patient year		Source and justification
	Responder	Non-responder	
			One clinician said they would like to see symptomatic patients more often than four times per year if capacity allowed.[4]
Dermatology nurse visit	1.00	2.00	UK advisory board.[4]
Hospitalisation (inpatient; dermatology)	0.01	0.04	BOI study.[20] Age- and gender-adjusted values (from mild PN patients for responders and moderate-to-severe PN for non-responders); no change from UK advisory board.[4]
Day case	0.00	0.17	TA534.[5] Values based on secondary care case note review to characterise resource use in AD patients uncontrolled by current therapy.
Full blood count	0.00	3.00	TA534.[5] Values based on monitoring costs for systemic treatments in AD patients
Background medication	1.00	2.38	TA534.[5] Clinical opinion solicited for the appraisal in AD suggested that wash products as well as emollients should be considered in the economic modelling.
Phototherapy	1.00	1.20	TA534.[5] Included based on clinician feedback in PN global advisory board (April 2022) to include phototherapy costs.[26]
Psychologist	0	0.1	Assumption. Included based on clinician feedback in PN global advisory board (April 2022) to include psychologists in multidisciplinary teams to address the behavioural aspects of PN.[26]

Abbreviations: AD: atopic dermatitis; BOI: burden of illness; HCRU: healthcare resource use; PN: prurigo nodularis; UK: United Kingdom.

The resource use in Table 20 is used to define the annual number of each resource used in the dupilumab plus BSC and BSC alone arms of the model for responders and non-responders, where responders are assumed to incur reduced disease management costs compared to non-responders. Unit costs are applied to each resource use unit (Table 21) to estimate the total disease management costs by response status. The corresponding total cost per year used in the model is £1,359 for responders and £2,952 for non-responders (base case analysis). HCRU based on TA534 in AD was used in a sensitivity analysis (£1,789 for responders and £3,423 for non-responders).

Table 21 Health care resource unit costs used in the model (reproduced from CS Table 43, p100)

Health care resource	Unit cost, £	Source
GP consultation	39.23	PSSRU, 2021 (GP visit).[27] This is the unit cost of general practitioner visits, including direct care staff costs, with qualification costs, per-patient contact lasting 9.22 minutes.
Dermatology outpatient visit (consultant led)	183.96	The unit cost of a dermatologist visit was estimated to be the weighted average cost for consultant-led dermatology, non-admitted face-to-face follow-up (code WF01A) from the NHS Reference Costs 2020-21[28] (88%) and multi-professional non-admitted face-to-face follow-up attendance cost (12%). Weighting was based on UK market research derived from the previous CEM developed for dupilumab in AD (TA534).[5]

Health care resource	Unit cost, £	Source
Dermatologist nurse visit	27.50	PSSRU, 2021;[27] assuming 30 minutes of the hourly cost of a nurse of wage band 6
Emergency room visit	332.46	Weighted average unit cost of all A&E attendances where patients received treatment (not all A&E visits receive treatment). Assumes that PN A&E patients all receive treatment. Assumption taken from the Excel model developed previously by Sanofi for atopic dermatitis (TA534).[5] NHS Reference Costs 2020-21.[28]
Hospitalisation	2108.95	Value (£1795.29) taken from the model developed previously by Sanofi for AD, (TA534).[5] The value comes from an analysis of the HES database. The cost was inflated using consumer price inflation data from the ONS.[29]
Day case	710.57	Average of codes JD07A-JD07K, NHS Reference Costs 2020-21.[28]
Full blood count	3.63	National Schedule of NHS Costs 2020-2021; currency = DAPS05.[28]
Background medications	221.14	The cost of background medications was estimated by Sanofi (Appendix K). The data were obtained from the previous CEM developed for dupilumab in AD (TA534).[5] Clinical opinion solicited for this appraisal suggested that wash products as well as moisturisers should be considered in the economic modelling. Thus, the company states that their estimates about background medication use are conservative. Background medication cost was updated using December 2022 BNF data.[30]
Phototherapy	642.63	National Schedule of NHS Costs 2020-2021, day case, currency = JC47Z (dermatology) DAPS05.[28]
Psychologist	324.94	National Schedule of NHS Costs 2020-2021,[28] clinical psychology, consultant-led, non-admitted face-to-face.

Abbreviations: AD: atopic dermatitis; CEM: cost-effectiveness model; GP: general practitioner; HES: Hospital Episodes Statistics; NHS: National Health Service; ONS: Office for National Statistics; PSSRU: Personal Social Services Research Unit.

Points for critique

The EAG considers that, in general, the costs informing the model are appropriate but have noted some limitations. The first issue relates to the fact that the resource use may not accurately represent the true resources used by patients with moderate-to-severe PN in the NHS due to the challenges in clinical management, driven by difficulties in accurate diagnosis and lack of precise codes for PN, as outlined in the CS. Other issues relate to the costs of rescue medications, the costs of disease management associated with the number of hospitalisations, and adverse event costs for dupilumab.

Rescue medication costs

The EAG notes that the company used the frequency of rescue medications from participants in the PRIME2 and PRIME trials over a 24-week period as a proxy for long-term use of rescue therapies. The company combined information on the number of participants using rescue medications from the pooled trials with relevant acquisition costs, posology data and assumptions regarding the average duration of rescue treatment (see CS Table 42, p99). Given the EAG's concern about the limited generalisability of the PRIME trial populations to the NHS population, and the greater adherence to treatments in the protocol-driven trial setting, the EAG believes it is unlikely that the frequency and type of rescue medications used in the trials are a good proxy for long-term use in the NHS. The EAG

clinical advisers suggested that in routine clinical practice, there is likely to be at least half of patients with moderate-to-severe PN using systemic therapies such as methotrexate, but in the PRIME trials only one patient received methotrexate in the placebo arm as it was a prohibited medication.

At EAG points for clarification, the EAG noted that the frequency of rescue medications from participants in the PRIME2 and PRIME trials over a 24-week period was incorrectly implemented in the company's model. In the model, the company assumed that the medications used in the trials was over a 12-week rather than 24-week period. In response to the points for clarification, the company presented updated cost-effectiveness results for the base case analysis with this error corrected; the resulting impact on the cost-effectiveness results was minimal (see Section 5.1.1).

> ***item 13. The long-term frequency and type of rescue medications used in the PRIME trials is unlikely to represent that used in UK clinical practice.***

Disease management costs

The EAG first compared the health care resource use values for PN with those used in TA534 for AD. The EAG noted very little difference in frequency of resource use between the two conditions, except for the frequency of hospitalisations. The frequency of hospitalisations for PN was based on data from the BOI study rather than TA534 because PN patients are not predisposed to eczema herpeticum in the way that AD patients are. Therefore, the company assumed that hospitalisations for PN is a rare event compared to AD. In the BOI study, separate estimates of inpatient hospitalisations were provided (see CS Table 33, p91): one for inpatient hospitalisation (dermatology), and the other for inpatient hospitalisation (PN specific primary). The company used inpatient hospitalisation for dermatology in the model, which is associated with two times higher frequency compared to the PN-specific inpatient hospitalisation. The EAG considers it is more relevant to use the PN-specific inpatient hospitalisation frequency in the model; however, the impact on the cost-effectiveness results in minimal. The EAG clinical advisers indicated that hospitalisations for PN are very rare.

The unit cost of hospitalisation is based on that used in TA534; however, these hospitalisations are associated with erythrodermic eczema, which is rare for untreated PN. Furthermore, the CS states that the hospitalisation cost was considered too high at the global advisory board meeting in April 2022.[26]

> ***item 14. The frequency of hospitalisations and unit cost used in the model may be overestimated.***

AE costs for dupilumab

The EAG notes the recent MHRA warning on dupilumab which has been linked to side effects affecting the eye (Section 3.2.2.5). The guidance recommends that patients who develop conjunctivitis or dry eye that does not resolve following initial treatment, or patients with signs and

symptoms suggestive of keratitis (especially eye pain and vision changes), undergo ophthalmological examination. The model used the GP visit cost plus the outpatient ophthalmology attendance cost to calculate the costs associated with infectious conjunctivitis. However, the EAG considers there may be costs associated with surveillance and drug use for patients with the severe ocular side effect, but the incidence rate of this side effect in patients with moderate-to-severe PN is not known.

item 15. The adverse event costs for dupilumab may be underestimated if there are additional monitoring costs associated with the severe ocular side effect.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Summary of company's submission

All analyses presented in the CS include the confidential PAS discount for dupilumab. The base case cost-effectiveness analysis incorporates utility data from the PRIME2 and PRIME trials collected using the EQ-5D-5L instrument and valued using the UK tariff. A summary of the inputs and variables used in the company's base case analysis is presented in the CS, Table 49, p103.

Table 22 shows the company's updated base case probabilistic and deterministic cost-effectiveness results (reported in the company's response to EAG points for clarification with the error corrected in the costs of rescue medications). The probabilistic ICER for dupilumab plus BSC relative to BSC alone is £26,974/QALY, while the deterministic ICER is £27,009/QALY. The cost effectiveness acceptability curve is presented in the CS, Figure 18, p108.

Table 22 Company's updated base case results (adapted from Table presented on page 47 of company's response to EAG points for clarification)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Probabilistic							
BSC	[redacted]	[redacted]	[redacted]				
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,974
Deterministic							
BSC	[redacted]	[redacted]	[redacted]				
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,009

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Points for critique

The results of the company's updated base case are very similar to the company's original model, with the correction to the error in the calculation of rescue medication costs increasing the deterministic ICER by £130/QALY. The company did not submit a revised version of the model. The EAG reproduced the company's corrected base case analysis but noted a very minor discrepancy in the results (

Table 23).

Table 23 EAG's corrected base case deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Deterministic							
BSC	[redacted]	[redacted]	[redacted]				
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,010

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

To aid understanding of the key drivers of the cost-effectiveness results, Table 24 and Table 25 provide a summary of the disaggregated costs and QALYs, respectively. The additional costs of dupilumab plus BSC compared to BSC alone are driven by the drug acquisition costs of dupilumab, with some of this cost offset by lower disease management costs associated with a greater number of responders to dupilumab plus BSC versus BSC alone. The QALY gain for dupilumab plus BSC is driven by the gains in HRQoL associated with responders and the difference in QALYs between non-responders to dupilumab plus BSC and BSC alone.

Table 24 Summary of the disaggregated costs in the company's updated deterministic base case results

Item	Cost of dupilumab + BSC (£)	Cost of BSC (£)	Incremental costs (£)	% of total incremental costs
Dupilumab acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
BSC acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]
Rescue medication cost	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	[redacted]	[redacted]	[redacted]	[redacted]
Disease management cost	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; BSC: best supportive care.

Table 25 Summary of the disaggregated QALYs in the company's updated deterministic base case results

Item	QALYs of dupilumab + BSC (£)	QALYs of BSC (£)	Incremental QALYs (£)	% of total incremental QALYs
Baseline to week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 24+: Responders	[redacted]	[redacted]	[redacted]	[redacted]
Week 24+: Non-responders	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC: best supportive care; QALYs: quality-adjusted life years.

5.2 Company's sensitivity analyses

5.2.1 Summary of company's submission

The company conducted univariate deterministic sensitivity analysis (DSA) on a wide range of model inputs and plotted the ten most influential parameters on a tornado plot (see CS Figure 20, p108). These results indicate that the most influential parameters on the ICER results at a £30,000 threshold is baseline utility.

The CS reports twelve scenario analyses as summarised in Table 26. Note that the company did not present updated results for the scenario analyses with the error in rescue medications corrected. All the scenarios show dupilumab plus BSC is associated with ICERs of less than £30,000 per QALY gained.

No subgroup analyses were conducted by the company.

Table 26 Results of company's scenario analysis (reproduced from CS Table 52, p109)

Scenario	Rationale	Incremental costs	Incremental QALYs	ICER
Response criteria: WI-NRS improvement ≥4	Testing sensitivity to alternative response criteria	[redacted]	[redacted]	28,210
No response waning applied	Testing sensitivity to inclusion of response waning	[redacted]	[redacted]	26,851
Response waning AD Dermatologist survey + SEE	Testing sensitivity to values of response waning	[redacted]	[redacted]	28,082
Response waning AD Dermatologist survey + NICE estimates	Testing sensitivity to values of response waning	[redacted]	[redacted]	28,262
Response waning AD OLE study + SEE	Testing sensitivity to values of response waning	[redacted]	[redacted]	26,544
Inclusion of societal perspective	Testing sensitivity to inclusion of productivity loss	[redacted]	[redacted]	12,158
HCRU – AD micro-costing	Testing sensitivity to alternative cost values	[redacted]	[redacted]	26,661
HCRU – PN micro costing based on 2019/2020 cost data	Testing sensitivity to alternative cost values	[redacted]	[redacted]	27,652
HCRU-TA814	Testing sensitivity to alternative cost values	[redacted]	[redacted]	27,389
HCRU-TA534	Testing sensitivity to alternative cost values	[redacted]	[redacted]	23,255
Utility algorithm: Van Hout	Testing sensitivity to alternative utility values	[redacted]	[redacted]	24,148
AD discontinuation rate	Testing sensitivity to discontinuation assumptions	[redacted]	[redacted]	26,218

Abbreviations: AD: atopic dermatitis; HCRU: healthcare resource use; 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 numeric rating scale.

5.3 Model validation and face validity check

5.3.1 Summary of company submission

The company undertook both clinical and technical validation of the model. Expert clinical input was sought to validate the model structure, response criteria, all-cause discontinuation rates, long-term effect and response waning, calculation of utility values based on linear regression equations, treatment cost categories and HCRU for patients with moderate-to-severe PN. This is described in detail in Section B.3.10.1 of the CS.

For technical validation, the model was subject to processes in accordance with guidelines from the International Society for Pharmacoeconomics and Outcomes Research Society and the Society for Medical Decision-Making Joint Task Force for Modelling Good Research Practices,[31] based on testing face validity (confirming the model approach, data sources and assumptions with experts), internal validity (quality-checking of parameter values and calculations) and external validity (comparing model results with other published studies).

Points for critique

The EAG considers that the company's validation procedure was appropriate. The EAG reviewed the company model in detail. The EAG considered the model to be well coded and presented in a clear and transparent manner that did not hinder model validation. The EAG identified one minor error in the calculation of costs for rescue therapy medications, which the company corrected in response to EAG points for clarification.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

A summary of the main issues identified and critiqued in Section 4 along with the scenario where the EAG addresses each issue in its additional analyses is shown in Table 27. The EAG identified a number of limitations and areas of uncertainty in the company's cost-effectiveness analysis. Where possible, the EAG explored alternative assumptions and model inputs in the scenario analysis to the company's updated base-case analysis (EAG Scenarios 1-12). The EAG's base-case consists of the set of assumptions and model inputs that the EAG considers to be most appropriate for assessing the cost-effectiveness of dupilumab plus BSC relative to BSC alone. A thorough description of the EAG scenario analyses are presented in Section 6.1.1, while the impact on the cost-effectiveness results is presented in Section 6.2. The effect of making changes simultaneously on elements that are considered to form part of the EAG's preferred base case assumptions is presented in Section 6.3.

Table 27 Summary of the main issues identified by the EAG in Section 4 and EAG analyses

Critique item and description The EAG considers that:		Dealt with in the		Area of remaining uncertainty	Significant impact on ICER
		EAG Scenarios	EAG Base-case		
1	***A BSC treatment state, with utility values and costs weighted by the likelihood of response to BSC over time, is likely to better reflect fluctuations in response to standard treatment without dupilumab over time (e.g., from the use of systemic therapies). Ideally the model would discount any placebo effect from the results of the trials and then just model the true effect of BSC as the background treatment for all patients, including dupilumab non-responders.***	Sc. 2, 5-6	No	Yes	Yes
2	***A discontinuation rate for BSC responders is not required in the model because these patients remain on BSC treatment.***	Sc. 2	Yes	Yes	Yes
3	***Baseline population characteristics of age, weight, percentage of male, duration of PN, WI-NRS score, DLQI score and EQ-5D utility value in the PRIME trials may not match those seen in UK clinical practice.***	No	No	Yes	Unclear
4	***The treatment regimens used in the placebo arm of the pooled PRIME trials are unlikely to match that used for BSC in UK clinical practice.***	No	No	Yes	Unclear
5	***The EAG considers that the combined response criterion of WI-NRS improvement ≥4 from baseline and IGA-PN-S score of 0 or 1 at week 24 may be more relevant for assessing treatment response than the combined criterion of WI-NRS improvement ≥4 and IGA-PN-S reduction ≥1 because the former is consistent with the key endpoints used in the PRIME trials.***	Sc. 1	Yes	No	Yes
6	***The EAG considers an improvement in the DLQI to be important when considering adequate response to dupilumab in PN.***	No	No	Yes	Unclear
7	***The EAG does not consider it appropriate to include both an all-cause annual treatment discontinuation rate (that includes loss of response over time) and a probability of sustained response per year, for responders in the model.***	Sc. 3	No	Yes	Yes
8	***The annual treatment discontinuation rates are highly uncertain due to short trial follow-up and limited evidence.***	No	No	Yes	Unclear
9	***The probabilities of sustained response over time for both dupilumab plus BSC and BSC alone are highly uncertain due to short trial follow-up and limited evidence.***	Sc. 4-6	No	Yes	Yes
10	***The EAG does not consider it appropriate to apply separate utility values by treatment arm for non-responders because all non-responders receive BSC only in the model, and any treatment effect is expected to diminish upon discontinuation of treatment.***	Sc. 7-8	Yes	Yes	Yes
11	***The credibility of the results of the SEE for informing how HRQoL might evolve over the long-term for patients with moderate-to-severe PN when treated with either dupilumab plus BSC or BSC alone in NHS clinical practice is unclear.***	No	No	Yes	Unclear

Critique item and description The EAG considers that:		Dealt with in the		Area of remaining uncertainty	Significant impact on ICER
		EAG Scenarios	EAG Base-case		
12	***The EAG identified a number of inconsistencies in the company's approach to adjusting the utility values based on the results of the structured expert elicitation.***	Sc. 9-12	Partly	Yes	Yes
13	***The long-term frequency and type of rescue medications used in the PRIME trials is unlikely to represent that used in UK clinical practice.***	No	No	Yes	Not expected
14	***The frequency of hospitalisations and unit cost used in the model may be overestimated.***	No	No	Yes	Not expected
15	***The adverse event costs for dupilumab may be underestimated if there are additional monitoring costs associated with the severe ocular side effect.***	No	No	Yes	Not expected

Abbreviations: BSC: best supportive care; DLQI: Dermatological Life Quality Index; EAG: External Assessment Group; EQ-5D: EuroQol 5-Dimensions; HRQoL: Health-related quality of life; ICER: incremental cost-effectiveness ratio; IGA-PN-S: Investigator Global Assessment for Prurigo Nodularis-stage; NHS: National Health Service; OLE: open-label extension; PN: prurigo nodularis; SEE: structured expert elicitation; UK: United Kingdom; WI-NRS: worst-itch numeric rating scale.

6.1.1 Issues explored by the ERG in additional analyses

6.1.1.1 Scenario 1: Response rates based on the combined response criterion of WI-NRS improvement ⩾4 and IGA-PN-S score of 0 or 1 from baseline to week 24

As discussed in Section 4.2.6.1, the EAG considers that the combined response criterion of WI-NRS improvement ⩾4 from baseline and IGA-PN-S score of 0 or 1 at week 24 may be more relevant for assessing treatment response than the combined criterion of WI-NRS improvement ⩾4 and IGA-PN-S reduction ⩾1 because the former is consistent with the key endpoints used in the PRIME trials.

Scenario 1 assesses the cost-effectiveness of dupilumab plus BSC relative to BSC alone using the response rates reported in Table 13 for the composite response criterion of WI-NRS improvement ⩾4 from baseline and IGA-PN-S score of 0 or 1 at week 24, which were provided in the company's response to EAG points for clarification. The EAG considers this scenario in the EAG preferred base case assumptions.

6.1.1.2 Scenario 2: All-cause discontinuation rate for BSC set to 0%

As discussed in Section 4.2.6.2, the EAG considers that a discontinuation rate for BSC responders should not be implemented in the model as these patients remain on BSC treatment regardless of their response status. Instead, the EAG believes that the utility values and costs associated with BSC should be weighted by the likelihood of response to BSC over time. This is likely to better reflect fluctuations in response to standard treatment without dupilumab over time (e.g., from the use of systemic therapies).

Scenario 2 assesses the implications on the cost-effectiveness of dupilumab plus BSC relative to BSC alone when the all-cause discontinuation rate for BSC responders is switched off, i.e., set to 0% for responders to BSC treatment, but the response waning assumptions for BSC (25% of the responders would lose response in year 2, 50% in year 3, 75% in year 4, and 100% in year 5 and beyond) still holds as per the company's base case. The EAG considers this scenario in the EAG preferred base case assumptions.

6.1.1.3 Scenario 3: Response waning assumptions switched off

As discussed in Section 4.2.6.2, the EAG has a number of concerns regarding the assumptions used in the model for long-term treatment effect and response waning. The EAG is not entirely clear why both an all-cause annual treatment discontinuation rate (that includes loss of treatment response) and a probability of sustained response per year is used to model long-term response to treatment (both of which are implemented as a transition probability [additively] from the 'Response' to 'No response' treatment state in the model). The company states that the all-cause discontinuation rate is used to model loss of response, adverse events or patient/clinician preference, while the concept of response

waning is used to model the exit from the controlled clinical trial environment where the observed effect size for BSC alone would not persist once patients have completed the trials and are outside the protocol-driven clinical trial setting. However, it is not clear why further discontinuations associated with response waning are applied on top of the annual discontinuation rate because any benefit from improved adherence would be expected to be applied equally to both the dupilumab plus BSC and BSC alone arms of the clinical trials, which should not affect how the treatments perform relative to one another.

Scenario 3 assesses the implications on the cost-effectiveness of dupilumab plus BSC relative to BSC alone when the response waning assumptions are switched off for both treatment arms, while the all-cause annual discontinuation rates are assumed to hold as per the company's base case.

6.1.1.4 Scenario 4: Alternative estimates for maintenance of treatment effect for dupilumab plus BSC

In the absence of long-term data for dupilumab in PN, the CS uses data from the dupilumab in AD open-label extension study, which demonstrates that use of dupilumab over the longer term is associated with maintained or increased benefit in AD.[22] In the company's base case analysis, the probability of dupilumab plus BSC patients having a sustained response was based on the proportion of participants achieving EASI-75 (Eczema Area and Severity Index) outcome in AD of 91.4% in year 2, 97.2% in year 3 and 90.9% in year 4 and onwards. The EAG considers that the proportion of patients achieving ≥4-point reduction in weekly Pruritus Numerical Rating Scale (NRS) score from baseline in AD may be a more relevant outcome for PN because it represents a measure of itch intensity, with corresponding estimates of 65.7% in year 2, 64.8% in year 3 and 70.8% in year 4 and onwards.

Scenario 4 assesses the implications on the cost-effectiveness of dupilumab plus BSC relative to BSC alone when the maintenance of treatment effect for dupilumab plus BSC over the longer term is based on proportion of patients achieving ≥4-point reduction in weekly Pruritus Numerical Rating Scale (NRS) score from baseline in AD rather than proportion achieving EASI-75 outcome in AD.

6.1.1.5 Scenario 5-6: Response to BSC held constant over time

As discussed in Section 4.2.2.1 and under Scenario 2 above, the EAG considers that the utility values and costs associated with BSC should be weighted by the likelihood of response to BSC and therefore neither an all-cause discontinuation rate or response waning assumptions are required for BSC.

Scenario 5 assesses the implications on the cost-effectiveness of dupilumab plus BSC relative to BSC alone when the response rate at week 24 for BSC is held constant over time (i.e., discontinuation rate set to 0% for BSC and response waning assumptions for BSC switched off). This scenario reflects the extrapolation of the relative difference in response rates between dupilumab plus BSC and BSC alone

observed at week 24 in the trials over the long-term rather than the company's assumption that the response rate for BSC at week 24 is short lived and rapidly falls to 0% (due to the high discontinuation rate and response waning assumptions used for BSC), which results in a large difference in response rates between dupilumab plus BSC and BSC alone after week 24 (see Figure 3 and 4 for the Markov trace showing the proportion of responders and non-responders to dupilumab plus BSC and BSC alone, respectively).

Scenario 6 assesses the implications on the cost-effectiveness of dupilumab plus BSC relative to BSC alone when only 25% of the response rate at week 24 for BSC is held constant over time.

6.1.1.6 Scenario 7-8: Same utility value by treatment arm for non-responders

As discussed in Section 4.2.8.3, the EAG does not consider it appropriate to apply separate utility values by treatment arm for non-responders because all non-responders receive BSC only in the model, and any treatment effect is expected to diminish upon discontinuation of treatment. The EAG has a concern that most of the HRQoL improvement associated with treatment, as observed in the PRIME2 and PRIME trials, is a result of better adherence to treatments in the protocol-driven clinical trial setting, which is the justification used in the CS for treatment waning assumptions. In particular, the EAG notes that only a small difference in HRQoL is observed between treatment arms in responders to treatment, while a much larger difference is observed in participants in the trials who did not respond to either treatment by week 24. The company's base case analysis uses treatment arm-specific utility values for non-responders based on those observed in the trials at week 24. The EAG believes that the pooled (across treatment arms) week 24 utility value for non-responders would be more appropriate for all non-responders in the model at week 24 because these patients have not responded to treatment and the model assumes that dupilumab plus BSC non-responders receive BSC only. Furthermore, [redacted]

Scenario 7 assesses the implications on the cost-effectiveness of dupilumab plus BSC relative to BSC alone when the pooled (across treatment arms) week 24 utility value is applied for non-responders ([redacted]), while scenario 8 uses the week 24 utility value for BSC non-responders ([redacted]) for all non-responders in the model.

6.1.1.7 Scenario 9-12: Extrapolation of utility values for non-responders over time

As discussed in Section 4.2.8.4, HRQoL improvements for responders at week 24 are maintained for patients who continue to respond to treatment over time, whereas the utility values for non-responders (those who were non-responders at week 24 or who discontinued treatment at a later time point) are adjusted downwards over time. As noted above, the company's base case analysis uses treatment arm-specific utility values for non-responders, which are then adjusted down over time based on the results

of a SEE exercise. In addition to concerns about the credibility of the results of the SEE, the EAG noted a number of inconsistencies in the way that the results of the SEE were used to adjust the utility weights for non-responders. Importantly, the EAG noted that the utility values for dupilumab plus BSC non-responders when they move to BSC remain higher than the utility values for BSC, even after 5+ years loss of treatment response,

[redacted]. Scenarios 9 to 12 explore the impact of alternative assumptions for the extrapolation of utility values for non-responders over time.

In scenario 9, the utility values for dupilumab plus BSC non-responders are assumed the same as BSC non-responders, based on those presented in Table 16, i.e., the HRQoL benefits for dupilumab plus BSC diminishes to close to baseline utility after 2 years upon discontinuation.

In scenarios 10 and 11, the inconsistencies in the way that the results of the SEE were used to adjust the utility weights for non-responders are removed. In scenario 10, separate treatment arm-specific utility values for non-responders at week 24 are adjusted down based on the proportion of utility maintained over time from the results of the SEE for dupilumab non-responders (20% at 6 months, 5% at 1 year and 0% at 2+ years from Table 17) and BSC non-responders (10% at 6 months, 1% at 1 year and 0% at 2+ years from Table 17), whereas in the company's base case analysis the utility values for dupilumab non-responders at week 24 was adjusted down based on the SEE results for dupilumab responders (38% at 6 months, 18% at 1 year and 9% at 2+ years from Table 17).

In scenario 11, separate, treatment arm-specific utility values for non-responders are adjusted down based on the proportion of utility maintained over time from the results of the SEE but in this scenario the model distinguishes non-responders at week 24 from those who discontinue treatment and become non-responders at a later point in time. In this scenario, the utility weight for patients who lose treatment response with dupilumab plus BSC and become non-responders in the model, having previously responded to treatment at week 24, i.e., those classified as dupilumab responders in the SEE (Table 17), is based on adjusting down the utility weight of dupilumab plus BSC responders, since these patients were previous responders to treatment. Similarly, the utility weight for BSC responders who lose response to BSC and become non-responders in the model, having previously responded to BSC at week 24, is adjusted down based on the results of the SEE for BSC responders (i.e., 29% at 6 months, 15% at 1 year and 9% at 2+ years from Table 17). Table 28 summaries the utility values used for non-responders to treatment over time in Scenario 11.

Table 28 Utility values used in scenario 11 for non-responders to treatment over time according to time since becoming a non-responder and according to previous response status

Time since becoming a non-responder	Dupilumab plus BSC non-responder at week 24	Dupilumab plus BSC non-responder having previously responded at week 24	BSC non-responders at week 24	BSC non-responder having previously responded at week 24
0 – 6 months*	[redacted]	[redacted]	[redacted]	[redacted]
6 – 12 months	[redacted]	[redacted]	[redacted]	[redacted]
1 – 2 years	[redacted]	[redacted]	[redacted]	[redacted]
2+ years	[redacted]†	[redacted]	[redacted]†	[redacted]

Abbreviations: BSC: best supportive care.
*Assumed to have the same utility value at week 24 from the pooled trials.
†Close to baseline utility value.

In scenario 12, the 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 from month 6 onwards to reflect [redacted].

In this scenario, for the first six months, the pooled (across treatment arms) utility value for non-responders at week 24 is used for dupilumab plus BSC and BSC non-responders who did not respond to treatment by week 24 in the trials (i.e., [redacted]), while the utility value for dupilumab plus BSC and BSC non-responders who previously responded to treatment by week 24 in the trials but subsequently discontinued treatment and became a non-responder is used, i.e., [redacted] for dupilumab plus BSC and [redacted] for BSC for the first six months since becoming a non-responder, after which the utility value rebounds to baseline for all non-responders.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 29 shows the results of the EAG scenarios. The EAG scenario with the largest impact on the ICER is scenario 5 where the response rate for BSC at week 24 from the trials is held constant over time. This scenario may be considered favourable towards BSC but it more accurately reflects the extrapolation of the relative difference in response rates between dupilumab plus BSC and BSC alone observed in the trials over the long-term rather than the company's assumption that the response rate for BSC is short lived and rapidly falls to zero after week 24. It is also worth noting the EAG concerns that the BSC therapies used in the trials are much more conservative than those commonly used in NHS practice, where systemic immunosuppressants, antihistamines and oral steroids were prohibited medications and high- or super-potent TCS were only allowed as rescue therapy. Therefore, higher response rates associated with BSC may be expected in practice compared to those observed in the trials.

The implications of the company's assumption that the response rate for BSC is short lived and rapidly falls to zero is also shown in scenarios 2 and 3. In scenario 2, the discontinuation rate for BSC is set to 0% but the response waning assumptions for BSC remain (i.e., 25% of the responders would lose response in year 2, 50% in year 3, 75% in year 4, and 100% in year 5 and beyond). In scenario 2 the ICER increases from the company's base case ICER of £27,010 to £29,026, which highlights the importance of this assumption. In scenario 3, the response waning assumptions are switched off for both treatment arms, but the high annual discontinuation rate for BSC of [redacted] remains (compared to [redacted] for dupilumab plus BSC), which increases the ICER from £27,010 to £28,822.

The other EAG scenarios that have a large impact on the ICER are those relating to the utility values (scenarios 7-12). Scenarios 7 and 8 demonstrate that the utility difference between dupilumab plus BSC non-responders and BSC alone non-responders at week 24 in the trials is a key driver of cost-effectiveness. The company's base case uses treatment arm-specific utility values for non-responders at week 24 but the difference in utility between treatments in participants who did not respond by week 24 (i.e., [redacted]) is much larger than the difference in utility between treatments in responders at week 24 (i.e., [redacted]). In scenario 7, the pooled (across treatment arms) week 24 utility value for non-responders increases the ICER to £29,176, while setting the utility value for dupilumab plus BSC non-responders equal to BSC non-responders increases the ICER to £29,919.

Scenarios 9 to 12 demonstrate that the utility waning assumptions for non-responders, where the utility values for non-responders are adjusted down over time, are a key driver of cost-effectiveness. In these scenarios, the ICER increases to between £28,896 and £32,763. Of these scenarios, the EAG considers scenario 12 to be most appropriate (ICER = £32,763) where the 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, whilst also distinguishing a difference in utility between those who did not respond to treatment by week 24 and those who responded by week 24 but subsequently discontinued treatment and became a non-responder.

Scenarios 1 and 4 also demonstrate a large impact on the ICER by decreasing it from £27,010 to £25,279 (scenario 1) and £24,629 (scenario 4). In scenario 1, the alternative response criterion of WI-NRS improvement $\geq$4 and IGA-PN-S score of 0 or 1 is used instead of WI-NRS improvement $\geq$4 and IGA-PN-S reduction $\geq$1 from baseline to week 24. Although the efficacy results for the alternative response criterion from the trials is less favourable towards dupilumab plus BSC, in terms of the relative difference in response rates between dupilumab plus BSC and BSC alone (see Table 12 and Table 13), the ICER decreases from the company's base case ICER. The reason for the decrease is that although the response rate to dupilumab plus BSC is lower under the alternative response criterion, the non-responders to dupilumab plus BSC are benefiting from the larger utility difference

associated with dupilumab plus BSC non-responders compared to BSC non-responders over time, while the total costs associated with dupilumab plus BSC falls due to lower drug acquisition costs associated with non-response. Importantly, this demonstrates that the relative difference in the response rates observed in the trials for dupilumab plus BSC compared to BSC alone at week 24 for the different response criteria is less important for the cost-effectiveness of dupilumab plus BSC in the company's model because the company assumes a higher utility value for dupilumab plus BSC non-responders compared to BSC non-responders (even though all non-responders receive BSC only), whilst also assuming that the response rate for BSC rapidly falls to 0%. This effect is also demonstrated under scenario 4 where the probability of maintaining response to dupilumab plus BSC over time is lower than the company's base case assumptions, but yet the ICER decreases from the company's base case ICER for the same reasons as scenario 1.

Table 29 Cost-effectiveness results of the EAG scenario analyses

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company's base-case	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£27,010
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
1	Response criteria: WI-NRS improvement ≥4 and IGA-PN-S score of 0 or 1 from baseline to week 24	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£25,279
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
2	All-cause discontinuation rate for BSC set to 0%	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£29,026
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
3	Response waning assumptions switched off	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£28,822
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
4	Alternative estimates for maintenance of treatment effect for dupilumab plus BSC	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£24,629
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
5	Response to BSC at week 24 held constant over time	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£106,039
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
6	25% of the response rate for BSC at week 24 held constant over time	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£27,816
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
7	Same utility value by treatment arm for non-responders based on week 24 pooled value for non-responders	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£29,176
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
8	Same utility value by treatment arm for non-responders based on week 24 value for BSC non-responders	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£29,919
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
9	Utility waning rates for dupilumab plus BSC non-responders set equal to BSC non-responders	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£32,714

		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
10	Separate utility waning rates by treatment arm for non-responders based on the results of the SEE	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£32,343
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
11	Separate utility waning rates by treatment arm for non-responders based on the results of the SEE and according to response status at week 24	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£28,896
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
12	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 from month 6 onwards	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£32,763
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-

Abbreviations: BSC: best supportive care; Dupi: dupilumab plus BSC; EAG: external assessment group; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; SEE: structured expert elicitation.

6.3 EAG's preferred assumptions

The ERG preferred assumptions are:

- Response rates based on the combined response criterion of WI-NRS improvement ⩾4 and IGA-PN-S score of 0 or 1 from baseline to week 24 rather than the combined criterion of WI-NRS improvement ⩾4 and IGA-PN-S reduction ⩾1 because the former is consistent with the key endpoints of the PRIME trials – Scenario 1.
- All-cause discontinuation rate for BSC set to 0% (still includes response waning on BSC) – Scenario 2.
- Pooled (across treatment arms) utility value at week 24 is used for non-responders, who were non-responders to treatment by week 24 in the trials – Scenario 7.
- 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. A distinction in utilities is also made between 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-responder. In the former case, the pooled utility value at week 24 is used for non-responders for the first six months (scenario 7), while in the latter case, the utility value for dupilumab plus BSC and BSC alone responders is used for the first six months since becoming a non-responder, after which the utility value rebounds to baseline for all non-responders – Scenario 12.

Table 30 shows the EAG's preferred assumptions, which form the EAG base case, while Table 31 shows the cumulative impact on the ICER. In Table 31 we also show the cumulative impact of scenarios 2, 7 and 12 with the response criterion of WI-NRS improvement ≥4 and IGA-PN-S reduction ≥ 1 from baseline to week 24 (company base case response criterion) rather than that used in scenario 1.

Table 30 Detailed cost-effectiveness results for the EAG preferred model assumptions

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company's base-case	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£27,010
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
1	Response criteria: WI-NRS improvement ≥4 and IGA-PN-S score of 0 or 1 from baseline to week 24	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£25,279
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
2	All-cause discontinuation rate for BSC set to 0% (includes response waning on BSC)	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£29,026
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
7	Same utility value by treatment arm for non-responders based on week 24 pooled value for non-responders	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£29,176
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
12	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. A distinction in utilities is also made between 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-responder in the model.	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£32,763
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-

Abbreviations: BSC: best supportive care; Dupi: dupilumab plus BSC; EAG: external assessment group; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio.

Table 31 Cumulative cost-effectiveness results for the EAG preferred model assumptions

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Company's base-case	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£27,010
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
1	Response criterion: WI-NRS improvement ≥4 and IGA-PN-S score of 0 or 1 from baseline to week 24	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£25,279
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
1+2	+ All-cause discontinuation rate for BSC set to 0% (includes response waning on BSC)	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£26,627
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
1+2+7	+ Same utility value by treatment arm for non-responders based on week 24 pooled value for non-responders	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£29,995
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
1+2+7+12	+ 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.	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£37,291
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-
2+7+12	With response criterion: WI-NRS improvement ≥4 and IGA-PN-S reduction ≥ 1 from baseline to week 24 (company base case)	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£35,592
		BSC	[redacted]	[redacted]	[redacted]	[redacted]	-

Abbreviations: BSC: best supportive care; Dupi: dupilumab plus BSC; EAG: external assessment group; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio.

6.4 Conclusions of the cost effectiveness section

The company submitted a *de-novo* model that adopted a decision tree structure to assess patients' response to treatment with dupilumab, as an adjunct to BSC, compared to BSC alone, and a Markov model to estimate long-term health outcomes and costs conditional on response to treatment. The EAG considers that the model structure is broadly appropriate to inform decision making but there are a number of limitations and areas of uncertainty.

For the model structure, the company created separate treatment states for BSC responders and BSC non-responders in the model although both receive the same BSC treatment, which resulted in the model requiring an additional assumption about long-term discontinuation on BSC, even though patients are not discontinuing BSC treatment. The EAG believes that response to BSC over time could be modelled by weighting the utility values and costs in a BSC treatment state by the likelihood of response to BSC to reflect fluctuations in response to standard treatment without dupilumab over time and applied in the model to both BSC and dupilumab plus BSC non-responders, who discontinue active treatment and continue on BSC only.

The EAG noted that the company used different response criterion from the key endpoints in the PRIME trials. The EAG preferred base case assumptions include the combined response criterion of WI-NRS improvement $\geqslant$4 and IGA-PN-S score of 0 or 1 from baseline to week 24 (Scenario 1). However, the EAG has concerns about the appropriateness of not considering a measure of improvement in quality of life (such as the patient reported DLQI) in the response criterion as WI-NRS and IGA-PN-S are not routinely used to assess response to treatment in UK clinical practice.

For long-term treatment effect, the EAG does not consider it appropriate to include both an all-cause annual treatment discontinuation rate (that includes loss of response over time) and a probability of sustained response per year, for responders in the model, since both are implemented as a transition probability (additively) from the 'Response' to 'No response' treatment state in the model. Moreover, the source used to inform both the annual treatment discontinuation rates and probabilities of sustained response per year are highly uncertain due to short trial follow-up and limited evidence. The EAG preferred base case assumptions include a discontinuation rate of 0% for BSC (Scenario 2) but with response waning assumptions for BSC (i.e., 25% of the responders would lose response in year 2, 50% in year 3, 75% in year 4, and 100% in year 5 and beyond).

There are a number of uncertainties in the utility values used for non-responders in the model; most notable is the very large difference in utility weights between dupilumab plus BSC and BSC alone non-responders at week 24 ([redacted]) compared to the difference between treatment arms in responders at week 24 ([redacted]). Firstly, the EAG does not consider it appropriate to apply separate utility values

by treatment arm for non-responders because all non-responders receive BSC only in the model, and any treatment effect is expected to diminish upon discontinuation of treatment. The EAG preferred base case assumptions include the pooled (across treatment arms) week 24 utility value for non-responders (Scenario 7). Secondly, the EAG has concerns about both the appropriateness and credibility of the results of the SEE for informing how HRQoL might evolve over the long-term for patients with moderate-to-severe PN when treated with either dupilumab plus BSC or BSC alone in the NHS. Thirdly, the EAG noted inconsistencies in the approach used by the company to downward adjust the utility values for non-responders. Importantly, the EAG notes that the utility values for dupilumab plus BSC non-responders when they move to BSC remain higher than the utility values for BSC, even after 5+ years loss of treatment response. The utility values and their extrapolation over time is one of the key drivers of the cost-effectiveness results (Scenarios 9-12).

The EAG preferred base case assumptions are listed in Section 6.3, and the EAG base-case ICER is £37,291/QALY, which is over £10,000/QALY compared to the company base-case ICER of £27,010/QALY. Other areas of uncertainty and limitations in the evidence base could not be fully explored by the EAG and the impact on the ICER remains unclear, as summarised in Table 27 particularly in relation to the generalisability of the trial populations to the NHS and the treatment regimens used for BSC in the NHS which are unlikely to match those in the placebo arm of the pooled PRIME trials.

7 SEVERITY MODIFIER

The severity modifier does not apply to dupilumab for treating moderate to severe prurigo nodularis.

8 REFERENCES

1. Sanofi. *Summary of product characteristics (dupixent)*. 2023. Available from: Https://www.Ema.Europa.Eu/en/documents/product-information/dupixent-epar-product-information_en.Pdf [accessed date unknown]

2. Medicines and Healthcare products Regulatory Agency. *Summary of product characteristics: Dupixent 300 mg solution for injection in pre-filled syringe*. London: MHRA; 2023. Available from: https://mhraproducts4853.blob.core.windows.net/docs/0a83703374a95f0715cec305c4152fb67cb5fcf1

3. Frølunde AS, Wiis MAK, Ben Abdallah H, Elsgaard S, Danielsen AK, Deleuran M, et al. Non-atopic chronic nodular prurigo (prurigo nodularis hyde): A systematic review of best-evidenced treatment options. *Dermatology* 2022;**238**:950-60.

4. Sanofi. *[Data on File] Advisory board notes (12 December 2022)*; 2022.

5. National Institute for Health and Care Excellence. *Dupilumab for treating moderate to severe atopic dermatitis (TA534)*; 2018. Available from: https://www.nice.org.uk/guidance/ta534

6. Grundel S, Pereira MP, Storck M, Osada N, Schneider G, Stander S, et al. Analysis of 325 patients with chronic nodular prurigo: Clinics, burden of disease and course of treatment. *Acta dermato venereologica.* 2020;**17**.

7. Klejtman T, Beylot-Barry M, Joly P, Richard MA, Debarbieux S, Misery L, et al. Treatment of prurigo with methotrexate: A multicentre retrospective study of 39 cases. *J Eur Acad Dermatol Venereol* 2018;**32**:437-40.

8. Chiricozzi A, Maurelli M, Gori N, Argenziano G, De Simone C, Calabrese G, et al. Dupilumab improves clinical manifestations, symptoms, and quality of life in adult patients with chronic nodular prurigo. *J Am Acad Dermatol* 2019;**83**:39-45.

9. Napolitano M, Fabbrocini G, Scalvenzi M, Nisticò SP, Dastoli S, Patruno C. Effectiveness of dupilumab for the treatment of generalized prurigo nodularis phenotype of adult atopic dermatitis. *Dermatitis* 2020;**31**:81-4.

10. Calugareanu A, Jachiet M, Tauber M, Nosbaum A, Aubin F, Misery L, et al. Effectiveness and safety of dupilumab for the treatment of prurigo nodularis in a French multicenter adult cohort of 16 patients. *J Eur Acad Dermatol Venereol* 2020;**34**:e74-e6.

11. Sanofi. *[Data on File] 2.7.3 summary of clinical efficacy (prurigo nodularis)- dupilumab (sar231893/regn668)*; 2022.

12. Gov.UK. *Dupilumab (Dupixent): risk of ocular adverse reactions and need for prompt management*. 2022. Available from: https://www.gov.uk/drug-safety-update/dupilumab-dupixentv-risk-of-ocular-adverse-reactions-and-need-for-prompt-management [accessed 19 April 2023]

13. Foley P, Kerdraon YA, Hogden JP, Shumack S, Spelman L, Sebaratnam DF, et al. Dupilumab-associated ocular surface disease: An interdisciplinary decision framework for prescribers in the australian setting. *Australas J Dermatol* 2022;**63**:421-36.

14. Mélanie H, Susan Ruyu Q, Eunice Y, Mathieu M, Patricia-Ann L. Characterising the chronicity of dupilumab-associated ocular surface disease: An analysis of a retrospective case series. *BMJ Open Ophthalmol* 2022;**7**:e000947.

15. Sanofi. *[Data on File] 2.7.4 summary of clinical safety (prurigo nodularis) - dupilumab (sar231893/regn668)*; 2022.

16. Adelphi Values. *[Data on File] Prurigo nodularis indirect treatment comparison feasibility assessment report*; 2022.

17. Agrawal D, Sardana K, Mathachan SR, Bhardwaj M, Ahuja A, Jain S. A prospective study examining the effect of selected topical and systemic drugs on pruritus grading system score and stat 6 expression in patients of prurigo nodularis. *Indian J Dermatol* 2021;**66**:638-44.

18. Hernández Alava M, Wailoo A, Pudney S, Gray L, Manca A. Mapping clinical outcomes to generic preference-based outcome measures: development and comparison of methods. *Health Technol Assess* 2020;**24**:1-68.

19. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;**15**:708-15.

20. Sanofi. *[Data on File] Healthcare database study to estimate prevalence and healthcare burden of prurigo nodularis*; 2022.

21. National Institute for Health and Care Excellence. *NICE health technology evaluations: the manual*. 2022. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741 [accessed date unknown]

22. Beck LA, Deleuran M, Bissonnette R, de Bruin-Weller M, Galus R, Nakahara T, et al. Dupilumab provides acceptable safety and sustained efficacy for up to 4 years in an open-label study of adults with moderate-to-severe atopic dermatitis. *Am J Clin Dermatol* 2022;**23**:393-408.

23. Office of National Statistics (ONS). *National life tables – life expectancy in the UK: 2018 to 2020*. 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2018to2020 [accessed date unknown]

24. University of York. *Structured expert elicitation resources (STEER)*. 2022. Available from: https://www.york.ac.uk/che/research/teehta/elicitation/steer/ [accessed 2 December 2022]

25. Ara R, Brazier J, Zouraq IA. The use of health state utility values in decision models. *Pharmacoeconomics* 2017;**35**:77-88.

26. RTI Health Solutions. *[Data on File] Health economic model for dupilumab in prurigo nodularis - advisory board meeting minutes (22 April 2022)*; 2022.

27. Jones KC, Burns A. *Unit costs of health and social care 2021*. Canterbury, Kent: Personal Social Services Research Unit, University of Kent; 2021. Available from: https://kar.kent.ac.uk/92342/

28. NHS England. *National schedule of NHS costs 2020/21*. 2022. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.england.nhs.uk%2Fwp-content%2Fuploads%2F2022%2F07%2F2_National_schedule_of_NHS_costs_FY20-21.xlsx&wdOrigin=BROWSELINK [accessed 19 April 2023]

29. Office of National Statistics (ONS). *Inflation tables. 2022. Customer price inflation time series (mm23). Cpih index 00: All items 2015=100*. 2022. Available from: https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/d7bt/mm23. [accessed 01 July 2022]

30. British National Formulary. *British National Formulary (BNF)*. 2022. Available from: https://bnf.nice.org.uk/ [accessed date unknown]

31. Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: A report of the ispor-smdm modeling good research practices task force--7. *Value Health* 2012;**15**:843-50.

APPENDICES

Appendix 1 EAG appraisal of evidence identification

EAG appraisal of clinical effectiveness evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	**Missing Search Strategies:** In the original company submission, no search strategies were included for the searches of clinicaltrials.gov. This was raised as a clarification question and subsequently provided in the company response but documented without a date. The company's response to clarification question C5 refers to two included studies not available on clinicaltrials.gov at the time of the search, but do not specify the date of the search or whether it was searched again at a later stage. This highlights why the date is important information. In the original company submission, no search strategies were included for the searches of conference proceedings in Table 3 (Appendix D). This was raised as a clarification question but the company appear to have assumed the EAG meant conference abstracts rather than conference proceedings and did not provide the strategies. **Unclear Database Segments and Years of Coverage**: In the original company submission, there was no data on the database segment, or years of coverage, for Medline via Ovid or Embase via Ovid. This was raised as a clarification question but the company appear to have misunderstood what was meant by database segment and years of coverage. **PRISMA Diagram Unclear**: In the original company submission, only the database searches appear in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram, even though evidence was sought from a range of other sources. Notably Appendix D, p. 13 describes findings of 2 randomised controlled trials (RCTs) on clinicaltrials.gov but these do not appear in the PRISMA diagram. It is not clear which exact sources were searched for the different study types (these are documented as RCT and non-RCT). This was raised as a clarification question. The company's response provided additional information, but this was too vague to answer the question with clarity.
Were appropriate sources searched?	YES	A good selection of relevant databases, conference proceedings, grey literature, Health Technology Assessment (HTA) and trials sources were used. In addition, supplementary searches were performed.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study types.
Were appropriate search terms used?	YES	Search terms were comprehensive.

Were any search restrictions applied appropriate?	YES	Animal studies and irrelevant paper types were removed.
Were any search filters used validated and referenced?	UNCLEAR	Various search filters were used but not referenced. There was no mention of whether filters were validated.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

EAG appraisal of cost-effectiveness evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	**Missing Search Strategies**: In the original company submission, no search strategies were included for the searches of professional organisations, healthcare organisation websites, National Health Service Economic Evaluation Database (NHS EED), or the School of Health and Related Research Health Utilities Database. This was raised as a clarification question and the company responded with strategies for NHS EED and the School of Health and Related Research Health Utilities Database. Further details were given on the searches of professional organisations and healthcare organisation websites, but these were not documented properly. In the original company submission, there were no strategies provided for the targeted literature review (TLR) of cost-effectiveness studies which is referred to on p. 61 of the CS. This was raised as a clarification question. In response, the company provided a PubMed strategy, but this was not documented properly, and the number of hits was not shown. **Unclear Databases and Platforms**: In the original company submission, there was no description of the platform EconLit or the Cochrane Library databases were searched on – these database are on numerous platforms. This was raised as a clarification question but the company did not provide details of the platforms these databases were searched on. The company reproduced tables that had been included in the original submission and responded to say that no hits were identified from either database. However, these strategies cannot be scrutinised for errors because the platform was not stated. **PRISMA Diagram Unclear**: In the original company submission, only the searches of Embase, PubMed and Cochrane appeared in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram, even though evidence was sought from a range of other sources. These were all lumped together as 'other sources' which wasn't very descriptive for the reader. It would be better to state each source, followed by the number of relevant records found (if any). This was raised as a clarification question and the company responded with additional information in the form of tables. An additional PRISMA diagram was also provided but this contained figures that were inconsistent with the PRISMA diagram originally provided.
Were appropriate sources searched?	YES	A good selection of relevant databases was searched, including medical databases, specialised economics databases, websites of professional organisations, and healthcare organisation websites. In addition to this, supplementary searches of reference lists were undertaken.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy.

Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study types.
Were appropriate search terms used?	YES	Search terms were comprehensive.
Were any search restrictions applied appropriate?	YES	No restrictions were applied.
Were any search filters used validated and referenced?	UNCLEAR	Various search filters were used but not referenced. There was no mention of whether filters were validated.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

EAG appraisal of health-related quality of life evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	**Missing Search Strategies**: No search strategies were included for the searches of conference proceedings in Table 3 (Appendix D). This was raised as a clarification question but the company appear to have assumed that the EAG meant conference abstracts rather than conference proceedings and did not provide the strategies. **Unclear Database Segments and Years of Coverage**: There is no data on the database segment, or years of coverage, for Medline via Ovid or Embase via Ovid. This was raised as a clarification question but the company appear to have misunderstood what was meant by database segment and years of coverage. **PRISMA Diagram Unclear**: In the original company submission, only the database searches appear in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram, even though evidence was sought from a range of other sources. Notably Appendix D, p. 13 describes findings of 2 randomised controlled trials (RCTs) on clinicaltrials.gov but these do not appear in the PRISMA diagram. It is not clear which exact sources were searched for the different study types (documented as RCT and non-RCT). This was raised as a clarification question. The company's response provided additional information, but this was too vague to answer the question with clarity.
Were appropriate sources searched?	YES	A good selection of relevant databases, conference proceedings, grey literature, HTA and trials sources were used.
Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy.
Were appropriate parts of the PICOS included in	YES	The searches combined the population with the study types.

the search strategies?		
Were appropriate search terms used?	YES	Search terms were comprehensive.
Were any search restrictions applied appropriate?	YES	Animal studies and irrelevant paper types were removed.
Were any search filters used validated and referenced?	UNCLEAR	Various search filters were used but not referenced. There was no mention of whether filters were validated.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

EAG appraisal of cost and healthcare resource evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	**Missing Search Strategies**: In the original company submission, no search strategies were included for the searches of professional organisations, healthcare organisation websites, National Health Service Economic Evaluation Database (NHS EED), or the School of Health and Related Research Health Utilities Database. This was raised as a clarification question and the company responded with strategies for NHS EED and the School of Health and Related Research Health Utilities Database. Further details were given on the searches of professional organisations and healthcare organisation websites, but these were not documented properly. **Unclear Databases and Platforms**: In the original company submission, there was no description of the platform EconLit or the Cochrane Library databases were searched on – these database are on numerous platforms. This was raised as a clarification question but the company did not provide details of the platforms these databases were searched on. The company reproduced tables that had been included in the original submission and responded to say that no hits were identified from either database. However, these strategies cannot be scrutinised for errors because the platform was not stated. **PRISMA Diagram Unclear**: In the original company submission, only the searches of Embase, PubMed and Cochrane appeared in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram, even though evidence was sought from a range of other sources. These were all lumped together as 'other sources' which wasn't very descriptive for the reader. It would be better to state each source, followed by the number of relevant records found (if any). This was raised as a clarification question and the company responded with additional information in the form of tables. An additional PRISMA diagram was also provided but this contained figures that were inconsistent with the PRISMA diagram originally provided.
Were appropriate sources searched?	YES	A good selection of relevant databases were searched, including medical databases, specialised economics databases, websites of professional organisations, and healthcare organisation websites. In addition to this, supplementary searches of reference lists were undertaken.

Was the timespan of the searches appropriate?	YES	The original searches were not limited by date in the strategy.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the population with the study types.
Were appropriate search terms used?	YES	Search terms were comprehensive.
Were any search restrictions applied appropriate?	YES	No restrictions were applied.
Were any search filters used validated and referenced?	UNCLEAR	Various search filters were used but not referenced. There was no mention of whether filters were validated.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

Single Technology Appraisal

Dupilumab for treating prurigo nodularis (ID4054)

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 22nd June** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Imbalance in dropouts between treatment groups in the key clinical trials PRIME and PRIME2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 30 states "The PRIME2 and PRIME trials appear to have been well conducted with respect to internal validity, though there was an imbalance of dropouts between treatment groups, with significantly more patients dropping out of the placebo arm of both trials, primarily due to lack of treatment efficacy. "	We suggest this may be amended in line with our response provided during clarification.	We believe it is important to consider our response regarding imbalances in dropouts submitted at the time of clarification (please see analyses and justification provided to question A16). Please see conclusion of our response here: "As per the protocols and statistical analysis plans of the clinical trials, participants with missing data or those who received prohibited medications/procedures and/or rescue medications impacting efficacy were imputed as non-responders. Missing data are therefore not the only reason that a participant might be imputed as a non-responder. Use of prohibited/rescue medication was the most frequent reason and higher in placebo in both studies at both timepoints. Data of participants	Not a factual inaccuracy. Consideration was given to the company's response to EAG clarifications.

		taking the prohibited/rescue medication were set to missing after the medication usage and participants were imputed as non-responders in WI-NRS and IGA PN-S analyses. Other participants who were imputed as WI-NRS and IGA PN-S non-responders had mainly missing data due to premature discontinuation of study. They discontinued the study intervention due to lack of efficacy, AE or other reason and did not continue with the remaining study visits as suggested in the study protocols.“	

Issue 2 Application of utilities in the cost-effectiveness (CE) model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 50 states “Dupilumab is modelled to affect quality-adjusted life years (QALYs) by increasing the proportion	Based on clinical trial data observed in the two main clinical trials PRIME and PRIME2, dupilumab is modelled to affect quality-adjusted life years	We are concerned the original sentence implies that in our model we are favouring dupilumab with the current	Amended for increased clarity.

of patients who respond to treatment, which is associated with improved health-related quality of life compared to BSC. Non-responders to dupilumab are also modelled to have better quality of life than BSC, despite moving to treatment with BSC only. “	(QALYs) by increasing the proportion of patients who respond to treatment, which is associated with improved health-related quality of life compared to BSC. Non-responders of both arms are modelled to have arm specific quality of life based on clinical trial data, with better quality of life for dupilumab non-responder, despite moving to treatment with BSC only.	model structure, however we argue that the model was developed for PN based on the model structures previously developed and accepted in the analogous disease area of AD. We would like to highlight that the PN model patients on BSC arm are modelled separately in order to reflect the differences in utility achieved by those who respond to treatment and those who do not. We have used the best available evidence observed from the clinical trials to reflect this impact of treatment. It was observed during the studies that there was a difference in quality of life between dupilumab responders and BSC responders. Likewise, there was a difference in quality of life between dupilumab non-responders and BSC non-responders. We feel it is	

		important for the model to be aligned to the observed data and reflect any differences in treatment effect, possible uncertainties around these differences in the quality of life are assessed and considered in the sensitivity analyses.	

Issue 3 Description of introduction of dupilumab in the NHS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 50 states “The addition of dupilumab to BSC increases NHS costs due to its acquisition cost, with some of this cost offset by lower disease management and rescue medication costs associated with better treatment response compared to BSC. “	We suggest this should be rewritten to account for the significant benefits realised with dupilumab treatment.	We are concerned this sentence implies that dupilumab does not provide any benefits but on the contrary, places additional burden to the NHS. Therefore, we would like to emphasize that dupilumab offers significant benefits to patients and society, which are likely to be broader than those captured in the current CE model. We believe the submitted CE model is conservative from a cost	Not a factual inaccuracy. This sentence is specifically referring to the costs of dupilumab (the drug acquisition cost relative to other costs in the model). The previous (summary) sentence and other text throughout the report refers to the benefits of dupilumab.

		perspective and we would like to ask the EAG to consider this point and amend the highlighted sentence on page 50 and throughout the document.	

Issue 4 Modelling differences in quality of life observed in the clinical trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 51 states "Non-responders to dupilumab are also modelled to have better quality of life than BSC, despite moving to treatment with BSC only. "	Please consider amending this to note that this was the observed data. We suggest: "Non-responders to dupilumab are also modelled to have better quality of life than non-responders to BSC, based on clinical trial data."	We are concerned the original sentence gives the impression that in our model we are favouring dupilumab with the current model structure. We would like to highlight the model was developed for PN based on the model structures previously developed and accepted in the analogous disease area of AD. In line with the AD model, which was accepted by the Appraisal Committee, in the PN model patients on BSC arm are modelled separately	Amended as per issue 2 above.

		to reflect the differences in utility directly observed in the clinical trials by those who respond to treatment and those who do not. In the clinical trials, there is a difference in quality of life between dupilumab responders and BSC responders was observed. Likewise, there is a difference in quality of life between dupilumab non-responders and BSC non-responders.	

Issue 5 Structure and movement in the CE model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 52 states "The CS acknowledges that there is a chance that some patients could move from the 'No Response' to the 'Response' state for a short period of time due to symptomatic improvement on systemic therapies, but	We would like to suggest a clarifying statement is made within this sentence. "The CS acknowledges that there is a chance that some patients could move from the 'No Response' to the 'Response' state for a short period of time due to symptomatic improvement	We are concerned that the original sentence implies we decided not to model these improvements on purpose and to favour dupilumab. We would like to highlight the model structure was built in line with clinical expert opinion provided to us. We have highlighted this in our	Amended for increased clarity.

this transition is not modelled. “	on systemic therapies, but this - in line with clinical and health economist expert opinion provided to the company during advisory board discussions - transition is not modelled.”	company submission. We also would like to emphasize that the current model structure is conservative from a cost perspective. Please see section B.3.2.2 which states the following: “UK clinicians who participated in an advisory board (Section B.3.5.3) conducted by Sanofi in December 2022 endorsed the PN model structure. The clinicians acknowledged there is a chance some patients could temporarily achieve symptom improvement on systemic therapies, and thus move from the non-responder to responder treatment state for a short period of time. However, this treatment effect is expected to happen only in the short term and no long-term benefit is expected from treatment with systemic therapies. Thus, patients may move up from the ‘No response’ to ‘Response’ treatment state, but then will	

		eventually revert to the 'No response' treatment state. While the model could have been designed with a treatment sequence structure that would represent these step-ups and subsequent step-down to non-response, the benefits of the systemic therapies are likely to cancel out and the overall benefit remain the same. In addition, the clinicians thought it would be difficult to quantify the proportion of patients that would achieve temporary symptom improvement on systemic therapies, since they suggested that responses to conventional systemics are highly variable in patients with PN. Thus, there is a possibility of missing costs for non-responders in the comparator arm who could temporarily step up and potentially receive a more costly	

		treatment for a period of time. Therefore, experts concluded that the model structure is conservative from a cost perspective and acceptable from a health technology assessment agency perspective. Similarly, the expert panel on a global advisory board conducted by Sanofi in April 2022 said that the settings used in the model are 'standard' and in line with expectations. "	

Issue 6 Previous methotrexate use in the clinical trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 57 states "*Furthermore,* [redacted] *and only* [redacted] *of the PRIME cohort had previously used methotrexate, which is a key treatment used in the NHS.*	We would like to suggest a clarifying statement. Furthermore, [redacted]	We are concerned that the original sentence implies that we have not included patients with prior exposure to methotrexate and other conventional systemics which are part of a standard treatment pathway for the	Not a factual inaccuracy, but the additional information has been added to the EAR.

As a consequence, the EAG believes that the populations in the trials may represent an easier to treat population (i.e., more likely to achieve response to the key trial outcomes). "	[redacted] and only [redacted] of the PRIME cohorts had previously used methotrexate, which is a key treatment used in the NHS. As a consequence, the EAG believes that the populations in the trials may represent an easier to treat population (i.e., more likely to achieve response to the key trial outcomes). ***** of participants had prior exposure to non-steroidal immunosuppressants in the clinical trials (***** in the dupilumab group and ***** in the placebo group).	management of PN. We would suggest including the highlighted statement in the EAG report as a clarifying statement.	

Issue 7 Application of response criteria in the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 58 states "The efficacy response criteria are used to define which patients are responders to treatment at week 24 and continue on treatment, or discontinue treatment and	We suggest that the following clarifying text is added: "The efficacy response criteria are used to define which patients are responders to treatment at week 24. In the dupilumab + BSC arm, non-responders stop dupilumab while responders continue. In the BSC-only	This suggested addition provides clarity on how response definition is incorporated in the CE model. We would like to emphasize that only people on active treatment can discontinue treatment based on all cause	Amended for increased clarity.

move to the 'No response' state in the model. "	arm, both responders and non-responders continue BSC. In both model arms, non-responders move to the 'No response' state in the model."	discontinuation and not based on response rate.	

Issue 8 Variables included in the regression equation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 70 states "Utility weights for application in the model were generated by multiplying the coefficients from the mixed regression models by the mean baseline characteristics and mean DLQI and WI-NRS scores (estimated by adding mean change from baseline scores) of the base case population (the average population characteristics of the PRIME2 and PRIME trials). The treatment indicator was also applied and follow-up scores at week 24 distinguished between responders and non-responders in order to	We suggest a more concise and clear way to describe the handling of utility data would be as follows: "The utilities used in the model were derived by multiple linear regression with the following model EQ5D Utility = Intercept + Age at Baseline + Gender + Baseline EQ5D Utility + Baseline DLQI Score + DLQI Score at Follow-up + WI-NRS Score at Follow-up, where the values "at follow-up" were all estimated from the least squares mean change from baseline. The data for all variables were from the pooled PRIME2 and PRIME trials."	The original EAG sentence does not provide a list of the variables that are included in the regression equation, although we believe this is important. Also, the original EAG sentence states that "the treatment indicator was also applied". However, no treatment indicator is included in the regression equation. Treatment effect is captured via DLQI and WI-NRS scores at follow-up.	To avoid any confusion, this sentence has been deleted. The previous paragraph on page 70 provides the list of variables included in the regression equation. The description is based on Appendix 8 of the company's response to EAG points for clarification.

generate treatment arm specific utility weights, stratified by response to treatment at week 24."			

Issue 9 Application of utility values over time in the CE model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 73 states "Therefore, health-related quality of life improvements for responders at week 24 are maintained for patients responding to treatment over time until treatment discontinuation, i.e., the utility value of [redacted] for dupilumab plus BSC responders is held constant over time in the model until treatment discontinuation."	We suggest the following clarifying statement is added to this section: "For consistency, the model also assumed that utility for BSC responders would persist over time until discontinuation. Specifically, the utility values assigned were [redacted] for responders on dupilumab + BSC, and ***** for responders on BSC alone."	We believe it is important to highlight that in the model not only dupilumab responders were assigned a constant utility value. All responders (on dupilumab and on BSC) were assigned a constant utility value over time. We would like to apply the suggested changes because we are concerned the original sentence might imply, we favoured patients on dupilumab disproportionately.	Amended for increased clarity.